

The main title of the report, 'Summary of work activities', in a bold, white, sans-serif font, set against a blue background.The author's name, 'Erika A. Lindh', in a white, sans-serif font, positioned below the title.The subtitle of the report, 'European Public Health Microbiology Training Programme (EUPHEM), 2017 cohort', in a white, sans-serif font, positioned below the author's name.The section header 'Background' in a bold, blue, sans-serif font.

According to the European Centre for Disease Prevention and Control (ECDC) Advisory Group on Public Health Microbiology ('national microbiology focal points'), public health microbiology is a cross-cutting area that spans the fields of human, animal, food, water, and environmental microbiology, with a focus on human population health and disease. Its primary function is to improve health in collaboration with other public health disciplines, in particular epidemiology. Public health microbiology laboratories play a central role in detection, monitoring, outbreak response and the provision of scientific evidence to prevent and control infectious diseases.

European preparedness for responding to new infectious disease threats requires a sustainable infrastructure capable of detecting, diagnosing, and controlling infectious disease problems, including the design of control strategies for the prevention and treatment of infections. A broad range of expertise, particularly in the fields of epidemiology and public health microbiology, is necessary to fulfil these requirements. Public health microbiology is required to provide access to experts in all relevant communicable diseases at the regional, national and international level in order to mount rapid responses to emerging health threats, plan appropriate prevention strategies, assess existing prevention disciplines, develop microbiological guidelines, evaluate/produce new diagnostic tools, arbitrate on risks from microbes or their products and provide pertinent information to policy makers from a microbiological perspective.

According to Articles 5 and 9 of ECDC's founding regulation (EC No 851/2004) 'the Centre shall, encourage cooperation between expert and reference laboratories, foster the development of sufficient capacity within the community for the diagnosis, detection, identification and characterisation of infectious agents which may threaten public health' and 'as appropriate, support and coordinate training programmes in order to assist Member States and the Commission to have sufficient numbers of trained specialists, in particular in epidemiological surveillance and field investigations, and to have a capability to define health measures to control disease outbreaks'.

Moreover, Article 47 of the Lisbon Treaty states that 'Member States shall, within the framework of a joint programme, encourage the exchange of young workers.' Therefore, ECDC initiated the two-year EUPHEM training programme in 2008. EUPHEM is closely linked to the European Programme for Intervention Epidemiology Training (EPIET). Both EUPHEM and EPIET are considered 'specialist pathways' of the two-year ECDC fellowship programme for applied disease prevention and control.

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This report summarises the work activities undertaken by Erika A. Lindh, cohort 2017 of the European Public Health Microbiology Training Programme (EUPHEM) at the Istituto Superiore di Sanità, Rome, Italy.

All EUPHEM activities aim to address different aspects of public health microbiology and underline the various roles of public health laboratory scientists within public health systems.

## Pre-fellowship short biography

Erika has a MSc in Microbiology (2008) and a PhD in Medical virology (2015), obtained at the University of Helsinki. Her work with viral zoonoses started as an undergraduate student with the development and set up of diagnostic assays. She moved on to working on molecular epidemiology and surveillance of avian influenza viruses, her thesis subject, and finally to studying virus-host cell interactions as a postdoctoral research fellow. Before joining the EPIET/EUPHEM program, Erika worked in a clinical microbiology laboratory at a central hospital in Finland, and to satisfy her growing interest in public health, initiated MSc studies in the subject at London School of Hygiene and Tropical Medicine. Erika has a keen interest in combining basic research with public health interventions. She looks forward to continuing work in the field of public health, applying her skills in different disciplines, acquired during the years as a researcher and during this fellowship.

## Methods

This report accompanies a portfolio that demonstrates the competencies acquired during the EUPHEM fellowship by working on various projects, activities and theoretical training modules.

Projects included epidemiological investigations (outbreaks and surveillance); applied public health research; applied public health microbiology and laboratory investigation; biorisk management; quality management; teaching and public health microbiology management; summarising and communicating scientific evidence and activities with a specific microbiological focus.

The outcomes include publications, presentations, posters, reports and teaching materials prepared by the fellow. The portfolio presents a summary of all work activities conducted by the fellow, unless prohibited due to confidentiality regulations.

## Results

The objectives of these core competency domains were achieved partly through projects or activities (on-job services) and partly through participation in the training modules. Results are presented in accordance with the EUPHEM core competencies, as set out in the EUPHEM scientific guide<sup>1</sup>.

### 1. Epidemiological investigations

#### 1.1. Outbreak investigations

##### ***Salmonella Typhi outbreak in north-eastern Italy in 2017 during an international mass gathering – applying genomics to support the epidemiological investigation***

Supervisors: Alessandra Carattoli and Luca Busani

*Salmonella enterica* serovar Typhi is a globally spread, potentially fatal food- and water-borne pathogen. In Europe, about 600, mostly travel-associated cases are reported annually. In late summer 2017, an outbreak of *S. Typhi* occurred in north-eastern Italy in a remote mountainous area during an international mass gathering. The gathering endured for one month and attracted nearly 3000 participants. An outbreak investigation was initiated after linked cases were reported by other Member States in the ECDC Epidemic Intelligence Surveillance System (EPIS). The outbreak investigation was challenging due to the reluctance of participants to provide information and because of poor traceability of cases. Five probable cases were finally detected in different regions. A whole genome-based method adapted from a highly comprehensive genotyping framework was simplified and used for phylogenetic analysis and genotyping of the outbreak isolates.

<sup>1</sup> European Centre for Disease Prevention and Control. European public health training programme. Stockholm: ECDC; 2017. Available from: <http://ecdc.europa.eu/en/publications/Publications/microbiology-public-health-training-programme.pdf>

The simplified *S. Typhi* phylogeny accurately mimicked the original global high resolution phylogenetic tree. Implementing the genomic approach, the index case (reporting recent travel to India), one probable case and one probable secondary case were assigned to the same rare genotype, clade 2.2. Our analyses further showed that the outbreak was seeded by a single introduction from a South Asian-origin genotype 2.2 strain, not previously encountered in Europe. Together with a multi-national team and ECDC representatives, an epidemiological report was prepared, summarizing all relevant information from the affected countries (Einöder-Moreno et al., manuscript in preparation).

Cases were successfully linked using the genomics approach, which facilitated retrospective case finding and increased the accuracy of the outbreak investigation. Genomics can be highly useful to support outbreak investigations in challenging and international settings. Simplified, easily available genomic tools have increasing utility for public health microbiology laboratories

### **Training modules**

The EPIET/EUPHEM introductory course provided participants with the basic concepts of logistical and analytical approach to outbreak investigations, including the ten steps of an outbreak investigation. The Outbreak investigations-module taught fellows how to perform analytical epidemiological studies within outbreak investigations using various software packages. During the module fellows performed all steps involved in outbreak analysis from data entry and management to stratified analysis (using EpiData, Stata and Microsoft Excel) and implementation of control measures. The participants were also given practical training in when and how to perform analytical studies for an outbreak investigation, including descriptive, cohort and case-control studies. The Multivariable analysis-module provided a more comprehensive understanding of the principles of statistical analyses, and how to build an optimal model using linear, logistic, Poisson and Cox regression. The Management, Leadership and Communication in Public Health-module trained fellows in many aspects of management and collaboration including time management and team collaboration. In addition, an insight into the role and activities of the ECDC Epidemic Intelligence Surveillance System (EPIS) during international outbreaks was given.

### **Educational outcome:**

Participation in an outbreak investigation in challenging and international settings provided experience in international collaboration, including data sharing and collaborating for a joint paper. The work also included performing whole genome analyses on bacterial genomes, including the use of bacterial genome databases and software for management and analysis of bacterial sequence data. The outbreak provided a good practice in communication on different levels, from poster presentation and manuscript drafting to addressing hard to reach communities.

## **1.2. Surveillance**

### ***Evaluation of the enhanced surveillance system for Legionnaires' Disease***

Supervisors: Maria Cristina Rota and Patrizio Pezzotti

Legionnaires' disease (LD) is an important cause of community- and hospital-acquired pneumonia. The causative agent is a gram-negative bacterium of the genus *Legionella*, most commonly *Legionella pneumophila* serogroup 1. Elderly people, patients with underlying debilitating conditions or immunosuppression are at risk of developing severe pneumonia or multisystem manifestations. Natural and artificial aquatic environments are the major reservoirs of *Legionella*, typically cooling towers and water distribution systems in buildings, including hotels and hospitals. The Istituto Superiore di Sanità runs the enhanced national surveillance system for LD, that has been running since 1993. The objectives of the epidemiological and microbiological surveillance are to monitor LD disease trends, estimate LD incidence, identify risk factors, promptly detect epidemic outbreaks and to promote prevention and control by providing information. Data is collected through surveillance forms filled in for each case by the physicians and local and regional health authorities.

The Italian LD surveillance system was evaluated with the objectives to i. describe the surveillance data ii. evaluate the performance and usefulness of the surveillance system and iii. identify actions for increasing the sensitivity of the system. Using data entered during the period 2014-2018, the surveillance system was evaluated for a range of attributes: simplicity, data quality, representativeness, timeliness, sensitivity, usefulness and flexibility.

The enhanced surveillance system for Legionnaires' disease was found to be both well run and to serve its purpose. Based on our findings, recommendations were made for improvement and for meeting the challenges that the annually increasing number of notified cases are bringing.

While being relatively uncommon, LD has a high public health impact causing significant morbidity and mortality. Under-diagnosis and under-reporting are acknowledged issues in LD surveillance. Improving surveillance systems will enhance identification of people at risk, provide adequate data to inform investigation and control of cases and outbreaks, and to prioritize resources.

### ***Management of imported malaria cases to Italy: epidemiology and surveillance in a non-endemic country***

Supervisors: Carlo Severini and Daniela Boccolini

Human malaria is caused by parasites of the *Plasmodium* species, which are transmitted by the bite of *Anopheles* spp female mosquitoes. *P. falciparum* and *P. vivax* are mainly responsible for the considerable health burden globally, estimated to cause over 200 million cases in 2017. Endemic transmission occurs in large parts of the world and nearly all countries of Africa. Italy has a long history of heavy endemic transmission of malaria. As the result of a successful eradication program, malaria was finally eradicated from the country after the Second World War. Today, increasing travel and movement of populations is connecting malaria endemic and non-endemic countries. Limited local transmission may occur after a single introduction of the parasite if a competent vector population is abundant and the environmental and climatic conditions are permissive.

The Italian Ministry of the Health and the Istituto Superiore di Sanità are in charge of a passive surveillance system for imported malaria cases. The aim of the surveillance system is to provide: i. confirmation of diagnosis ii. continuous monitoring of the epidemiological situation iii. investigation of suspected locally acquired cases and planning and implementing vector control measures. In average, around 750 cases have been notified in Italy annually in the last years, most of whom report recent travel history to Africa (<http://www.epicentro.iss.it/malaria/epidemiologia-italia>). Autochthonous cases occur infrequently in Italy but because of the presence of competent *Anopheles* vector species, immediate actions are needed to investigate possible autochthonous cases and for implementation of vector control measures in areas at risk of transmission. During the period 1997-2017, a total of 30 suspected autochthonous cases have been investigated. Identified transmission routes include transfusion and organ transplantation, other nosocomial routes and possible transmission by the mosquito vector.

The national surveillance data from 2018, including 753 reported cases, was analysed and summarized with the aim to provide data to inform accurate formulation of prevention recommendations. Risk factors specific for Italian and foreign-born cases were identified. No suspected autochthonous cases requiring investigation were identified during the project. The secondary aim, to transfer competence in parasitology, was obtained through taking part in the different tasks of the surveillance system (data entry and analysis, microscopy and molecular analyses and entomological activities).

Malaria is the most important parasitic infection globally in terms of morbidity and mortality, and consequently it represents an important issue of public health concern. Non-endemic European countries regularly face imported cases and sporadic locally acquired cases may occur. Early and accurate diagnosis is key to effective malaria case management and surveillance.

### ***Training modules***

The EPIET/EUPHEM introductory course familiarised participants with the use of STATA for statistical analyses and in the development, evaluation and analysis of surveillance systems.

#### **Educational outcome:**

The fellow developed her understanding of the different activities and attributes of surveillance systems, including data entry, maintenance of databases, description and analysis of surveillance data using software packages for statistical analysis, formulation of recommendations and producing surveillance reports based on the data.

She gained hands on experience in differential microscopy in malaria diagnostics and an insight into the value of the different diagnostic approaches. The project provided further a hands-on introduction into *Anopheles* vector biology, entomological activities and the main intervention strategies when suspected autochthonous malaria cases are identified.

## **2. Applied public health microbiology research**

### ***Whole genome sequence analysis of the Italian 2017 outbreak Chikungunya viruses***

Supervisor: Giulietta Venturi

Chikungunya virus is an emerging mosquito-borne pathogen with a wide global distribution. The virus is a major public health problem causing severe morbidity in affected areas and poses a considerable risk for unaffected areas hosting competent vector populations. In the summer of 2017, Italy experienced a chikungunya virus outbreak that spread in the Lazio region and caused a secondary outbreak in Calabria, with a final case number of 436. To understand the underlying genetic and molecular features of the outbreak virus, viruses from mosquito pools and clinical samples were isolated in cell culture and subjected to whole-genome sequencing and genetic analyses.

Eight genomes isolated from human cases and mosquito pools from the two outbreak foci were characterized and shown to share a high sequence identity. A distinct substitution pattern in the Italian 2017 viruses (including mutations in E1, E2, and nsP4) was partly shared with Pakistani 2016 outbreak viruses. Our evolutionary analyses indicate that these two recent outbreaks and several geographically widely distributed, travel-associated viruses form a cluster of rapidly emerging, Indian-origin, Indian Ocean lineage-viruses. Their emergence calls for enhanced monitoring and strengthened preparedness measures, including vector control programs and raised awareness among general practitioners in countries potentially at risk.

### ***GBS neonatal infections in Italy, 2015-2018***

Supervisor: Roberta Creti

Group B *Streptococcus* (GBS) is the leading cause of neonatal sepsis and meningitis in both developing and developed countries. Two temporal forms of infant GBS has been defined, early-onset disease (EOD) occurs in children up to six days old while late-onset disease (LOD) presents in children aged 7 to 90 days old. EOD is the result of vertical transmission from recto-vaginally colonised mothers to the newborn and can be prevented through implementation of screening for maternal colonization and risk factors and intrapartum antimicrobial treatment strategies. Risk-factors for and route of transmission of LOD are less well understood, and effective prevention strategies are consequently missing.

The National reference laboratory for GBS at Istituto Superiore di Sanità maintains an epidemiological and microbiological database of invasive GBS. Data is retrieved using a questionnaire tailored for GBS surveillance, including demographic and clinical data on the infant and GBS screening, intrapartum antimicrobial prophylaxis (IAP) administration and delivery data on the mother. In 2015-2018, the passive surveillance system obtained data from 144 cases and bacterial isolates from 66 cases. Since the available population-based data from Italy remain scarce, our aim was to i. describe, analyse and discuss the invasive neonatal GBS cases reported in Italy the past four years ii. assess compliance to the recommended strategies for preventing EOD iii. identify possible factors contributing to occurrence of LOD and iv. to monitor GBS serotype distribution in EOD and LOD cases.

Late pregnancy screening for maternal colonisation and consequent antibiotic prophylaxis has successfully reduced the incidence rate of neonatal EOD. Our results show that cases could be further prevented by reducing missed opportunities for IAP (deviation from the CDC guidelines and national recommendations). Among our cases, prematurity was the single outstanding risk factor for developing LOD. In the absence of specific prevention measures for LOD, awareness need to be raised about the importance of hygiene in health care facilities and caregivers to protect the vulnerable early preterm and low birthweight infants during their first months of life. With a GBS vaccine in the horizon, accurate population-based data is needed, preferentially through enhanced surveillance, to inform disease prevention strategies and decision making.

### ***Training modules***

The EPIET/EUPHEM Introductory Course familiarised fellows with developing and presenting study protocols and identification of the public health added values of research results. The Management, Leadership and Communication in Public Health Module trained fellows in many aspects of management, collaboration and communication, including efficient presentation deliveries according to target audiences and formulating recommendations based on research findings.

### **Educational outcome:**

Introducing genomic tools to support epidemiological studies is gaining ground. Knowing how to extract the added value of genomic data can be challenging as well as translating genomic information into public health learning outcomes and recommendations. The fellow gained experience in communicating the findings and their implications from a public health perspective. The fellow further gained experience in identifying key findings and draw conclusions from surveillance data analyses and to finally formulate recommendations for specific target groups.

### 3. Applied public health microbiology and laboratory investigations

#### ***Phenotypic and molecular characterization of carbapenemase-producing *Klebsiella pneumoniae* from invasive infections in Italy in 2016***

Supervisors: Maria Del Grosso and Monica Monaco

The growing rate of antimicrobial resistant infections is a significant and acute threat to public health. In 2015, over 200 000, generally healthcare-associated, infections and nearly 11 000 deaths due to antibiotic-resistant strains were recorded in Italy. Over half of these infection were attributed to carbapenem or colistin resistant enteric bacteria. Since the emergence of carbapenem-resistant (CR) *K. pneumoniae* in Italy a decade ago, the epidemic has been maintained by the international clonal group (CG) 258, including sequence type (ST) 512 and 258. Recent epidemiological studies show however an international emergence of extensively drug resistant clones, including ST307 that is outcompeting CG258 in some settings. Understanding the temporal fluctuation of ST's and the resistome composition of isolates are of major interest at both the local and global level.

We performed a survey to study the molecular epidemiology of CR-*K. pneumoniae* and to monitor colistin-resistance among isolates collected in 2016 through the national antibiotic resistance surveillance program (AR-ISS) of Istituto Superiore di Sanità (the National Institute of Health in Italy). We characterized a panel of 157 consecutive non-replicate clinical isolates of invasive CR-*K. pneumoniae*, collected from hospital laboratories and sequenced by whole genome sequencing. The aim of this work was to explore the genetic diversity of a comprehensive collection of recent CR-*K. pneumoniae* by describing trends in the temporal distribution of STs, analysis of antibiotic resistance patterns at the phenotypic and genotypic level, and to compare current data with previous Italian and international data.

Our data shows that while ST512 remains the most common clone in Italy, a shift from the dominance of CG258 towards a polyclonal trend has occurred. The observation was demonstrated by high clonal diversity, including a countrywide distribution of the high-risk clones ST307 and ST101. KPC-carbapenemase production continues to be by far the most frequent mechanism of carbapenem resistance in Italy. Our study further confirmed the high proportion (40%) of colistin resistant strains among the Italian CR-*K. pneumoniae* isolates. The high proportion of resistant strains in Europe constitutes a great public health concern and threat to patient safety. This study improved our understanding of current CP-*K. pneumoniae* populations in Italy and allowed us to identify emerging clones.

#### ***Invasive *Haemophilus influenzae* type b (Hib) disease cases in children in Italy, after 20 years of routine use of conjugate Hib vaccines***

Supervisor: Marina Cerquetti

*Haemophilus influenzae* is a common colonizer of the upper respiratory tract of both adults and children and an opportunistic pathogen able to cause severe invasive disease. *H. influenzae* serotype b (Hib) is a major cause of bacterial meningitis in young children, causing significant morbidity and mortality in areas where routine infant immunizations are not used. In Italy, the Hib vaccine was introduced in to the national infant immunization program in 1999. Children in Italy are scheduled for Hib vaccination at ages 3, 5 and 11 months, the age where susceptibility for serious disease is at highest while the child's immune system is still immature and requires frequent priming. At highest, the vaccination coverage reached 96% in 2007 but has since decreased to around 93% in 2015 and risen again to over 94% in 2018 ([http://www.salute.gov.it/portale/temi/p2\\_6.jsp?lingua=italiano&id=811&area=Malattieinfettive&menu=vaccinazioni](http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=811&area=Malattieinfettive&menu=vaccinazioni)). Although the use of the conjugate Hib vaccine has been successful in drastically reducing the number of reported invasive Hib infections in Italy, a number of invasive Hib disease cases are seen annually either because of incomplete vaccination status or through true vaccine failure (TVF). Previous studies have identified amplification of the *capB* locus as a virulence factor and contributor to TVF.

The Italian National Surveillance of Invasive Bacterial Disease Program (hosted at Istituto Superiore di Sanità) collects data and clinical isolates of invasive *H. influenzae* isolates. During the years 2012-2018, 31 cases of invasive Hib disease in children (aged 0-17) were reported of which 24 bacterial isolates were obtained. Of these cases, 10 were defined as TVF. We performed both epidemiological and microbiological analyses of the cases with the objectives to i. assess factors associated with invasive Hib disease in different age groups ii. Assess factors associated with with TVF iii. assess vaccine effectiveness and iv. monitor microbial features, including copy number of the *capB* locus among invasive isolates.

We found that in the age group 6-35 months, 65% of invasive Hib occurred in unvaccinated children. Most of these cases would probably have been preventable through vaccination according to the national immunization scheme. In children >3 years, TVF was observed in nearly all cases and nearly half of the cases reported underlying

conditions. Multiple copies of *capb* were detected over all in 26% of the cases and in 30% of TVF cases. Importantly, according to our estimates, vaccine effectiveness of the hexavalent Hib vaccine is good (79%) among 3-17 year-olds in Italy, although the confidence interval is wide (95% CI 0-95%,  $p=0.10$ ). While the conjugate Hib vaccine has been highly successful in reducing the incidence of invasive Hib disease, continued monitoring of changes in Hib epidemiology and identification of population groups at risk remain important for a timely implementation of necessary preventive measures. The pathogenesis of Hib vaccine failure remains unclear and more studies on TVF are needed to improve our understanding of the mechanisms involved. Immunization according to the national guidelines remains the most effective way to prevent invasive Hib disease in young children.

### **Training modules**

The EPIET/EUPHEM introductory course allowed fellows to become familiar with the major public health issues related to the emergence of antimicrobial resistance and mechanism of acquisition of carbapenem resistance in Enterobacteriaceae, both by developing SOPs and by problem based learning. A highly comprehensive lecture on outbreaks of healthcare associated infections was given during the Outbreak investigation-module. The Vaccinology-module provided participants with knowledge and skills to understand and undertake projects and routine work in the area of vaccine preventable disease epidemiology, including vaccination programmes, evaluation of vaccination interventions (including effectiveness), methods to inform vaccine programme decision making and improvement of vaccination coverage.

### **Educational outcome:**

The fellow gained experience in *in vitro* and *in silico* bacterial typing methods as well as a close insight into the genomic features of antimicrobial resistance in *K. pneumoniae*.

Surveillance of a vaccine preventable disease in the post-vaccination era was an opportunity to observe and appreciate the impact of immunization programmes on public health and demonstrated the continued need and methods to monitor disease trends after implementation of routine vaccinations. The work provided further experience in identification of key findings from surveillance data analyses and formulation of recommendations for the appropriate target groups.

## **4. Biorisk management**

### **Risk assessment for laboratory work**

Supervisor: Marina Cerquetti and Annalisa Pantosti

A risk assessment form for work in microbiology laboratories during the breast-feeding period was developed. The form was designed to provide a description of factors including facilities, microbiological agents, hazardous agents, laboratory methods and planned precautionary measures to allow for a comprehensive evaluation of possible risks to mother and child imposed by the planned laboratory work. The form provides a base for assessment of risks related to laboratory work and can be adapted to different situations.

### **Certifications**

- International Shipment of Dangerous Substances (WHO, Feb 2018)

### **Training modules**

The Biorisk and Quality Management-module provided training in biorisk and quality control management with the overall aim to build capacity in the EU/EEA Member States. The main objectives were to train fellows in quality management in biomedical and public health laboratories according to ISO 15189, in international shipping of infectious substances and in identification and mitigation of biorisks.

**Educational outcome:**

The fellow developed an understanding of the importance of biorisk management and the requirements necessary to control risks associated with the handling, storage, and disposal of biological agents and toxins in laboratories, including BSL3 and BSL4 laboratories, as well as biosafety risk assessment and mitigation.

## 5. Quality management

### *External quality assessment of multi-drug resistant *Mycobacterium tuberculosis* drug susceptibility testing by WHO supranational reference laboratory*

Supervisor: Lanfranco Fattorini

*Mycobacterium tuberculosis* (MTB) is the most common causative agent of the disease tuberculosis (TB), an usually severe chronic infection in the lung. Control of MTB relies on effective detection of cases and treatment with a combination of antibiotics. The emergence of multidrug resistant (MDR) and extensively resistant (XDR) strains is a major challenge in combatting TB. Regular quality assessment of laboratory services assures that the changing diagnostic needs are continuously met. Proficiency tests are a fundamental part of this process of assessing diagnostic capability and are used to i. assess accuracy and timeliness of laboratory test ii. allowing for comparison of results between laboratories and iii. allowing for errors in methodology and laboratory practices to be identified.

The Italian National TB Reference Laboratory at Istituto Superiore di Sanità works within the WHO TB Supranational Reference Laboratory Network providing regular external quality assessments (EQAs) and consequent support to a number of National Reference Laboratories (NRLs) both in Italy and abroad. In 2018, we evaluated the laboratory capacity and preparedness to detect and characterize multi-drug resistant *Mycobacterium tuberculosis* in the NRLs of four Middle Eastern and Central Asian countries. Twenty pre-tested MDR-MTB samples were cultivated and shipped to the participating laboratories. The performance of each NRLs was evaluated by their ability to identify MTB and associated phenotypic or genotypic antibiotic resistance to eight antibiotics (both first and second line). The results were analysed for sensitivity, specificity, predicted value for resistance, predicted value for susceptibility, accuracy and reproducibility according to the procedures endorsed by WHO. In the case that a laboratory's performance was found to be weak in any of the above-mentioned aspects, recommendations for improved performance would be made and the laboratories offered support depending on individual needs.

The overall performance of the laboratories was found good with only one country experiencing difficulties in testing for ethambutol susceptibility. A major issue was however the fact that only two countries delivered results for genotypic testing and three countries performed phenotypic testing of second-line drugs. EQAs are an essential part of laboratory quality management systems, ensuring reliable results for patients, physicians and health authorities. The lack of laboratory and diagnostic capacity is a recognized barrier for the implementation of an effective response to the challenges of drug resistant TB as well as for the surveillance of antibiotic resistance.

### *B. Training modules*

The Biorisk and Quality Management-module familiarised participants with different aspects concerning quality management, including both internal and external quality control. The module provided training in handling and packaging infectious substances of different categories and international shipping of dangerous substances according to the regulations of the International Air Transport Association (IATA).

**Educational outcome:** The fellow learned how to apply the principles and practice of shipping infectious substances according to current international regulations. Additionally, she learned how to apply the concepts of accreditation procedures, quality audits and validation of laboratory methods.



## 6. Teaching and pedagogy

### *Sexually transmitted disease – information booklet for youth*

Supervisors: Barbara Suligoj and Maria Cristina Salfa

Adolescence is a time when a young person undergoes substantial physical, emotional and social maturation. It is the time when sexuality is being explored, yet the understanding of the impact of sexual health may be difficult to perceive. Given the importance of sexually transmitted infections (STIs) as a public health issue, addressing this group with accurate, clear and non-judgmental information is of substantial importance.

In a joint effort to fill the gap of easily accessible material addressing youth on sexually transmitted disease, experts from the Istituto Superiore di Sanità teamed up with the Istituto Pasteur Italia and the IBSA foundation for scientific research, to write a non-profit openly available book to be distributed in schools and on the web. The book is written specifically addressing youth (aged 14-18), with the aim to provide them with basic information on STIs in an easily approachable way and tools to recognize and deal with a suspected infection. Great care has been taken in the original version to deliver the messages in a clear yet non-judgmental way. The original Italian booklet was very well received and subsequently a request for an English version to reach a wider audience was made by stakeholders. The book was translated from Italian to English with the aim to provide a low threshold, clear and friendly source of information on sexual health for adolescents. The final translation will be made freely available online in forums frequented by youth.

STIs have a great public health impact and may have long-lasting debilitating consequences if left untreated. Providing youth with accurate yet non-judgmental information on their sexual health is a public health responsibility: it will prevent infections through providing tools for the young to protect themselves and their near ones, help to overcome the stigma often associated with STIs and improve the individual's ability to seek health care in case of risk behaviors or exposures.

### *Whole genome sequence data management and analysis tutorials for peers*

The fellow provided tutorials to support the National Influenza Reference Laboratory in the transition from Sanger sequencing to whole genome-based sequencing and data management. The tutorials included assessment of objectives, assessment of learning needs, planning and producing material, delivering the tutorials and assessment of outcomes.

### *Serology lecture for epidemiologists, Vaccinology module*

The fellow prepared and delivered a lecture on serological diagnostic methods and interpretation of serological results to EPIETs during the Vaccinology-module (2019).

### *Problem Based Learning: Lecture on mechanisms of acquiring antimicrobial resistance by Enterobacteriaceae*

A lecture was prepared in a group on the mechanisms of acquisition and action of antimicrobial resistance in clinically relevant *Enterobacteriaceae*. The lecture was presented during the Introductory Course (2017) to fellow EUPHEMs.

#### **Educational outcome:**

The fellow received valuable experience in developing teaching materials and delivering educational information. She learned how to assess learning needs, plan for target audience directed content of educational material, delivery of educational information and finally to assess learning outcomes in the target group.

## 7. Public health microbiology management

### *Management of projects and meetings*

Public health microbiology management was an integral part of all projects and activities throughout the fellowship. Daily work involved planning and coordination of projects, time-management, setting up meetings and teleconferences, forming consensus decisions within research teams and communicating with multidisciplinary teams of experts. Final results and outputs were communicated to various audiences both orally and in written form.

### *Whole genome sequencing for surveillance and outbreak investigations in Italy*

As part of the Management, Leadership and Communication in Public Health-module, the fellows were invited to give a 3-minute presentation to ECDC leaders on the capacity of the hosting member state to perform whole genome sequencing (WGS) for surveillance and outbreak investigation. The fellow assessed current methods, needs and opinions on the use of WGS in reference laboratories at the training site (Istituto Superiore di Sanità (ISS, the Italian National Institute of Health) and summarized the findings for the panel of invited ECDC leaders.

### *Training modules*

The Management, Leadership and Communication in Public Health-module, provided an introduction to the principles of effective management and different management, motivation and leadership styles, to appreciate the role and responsibilities of leaders, managers and different EU agencies within the public health environment. The module provided tools to recognize and understand personality traits relevant to professional development and management tasks. Training on communication styles adapted for target audiences, ranging from different stakeholders to media and the public was given.

#### **Educational outcome:**

The fellow gained valuable experience in team building, management of conflicting of interests and negotiation skills from working in multidisciplinary teams. She further increased her understanding of the roles and responsibilities of different actors in public health settings, different management styles, team motivation, conflict management and the value of constructive feedback.

## 8. Communication

### **Publications**

1. Lindh E, Argentini C, Remoli ME, Fortuna C, Faggioni G, Benedetti E, Amendola A, Marsili G, Lista F, Rezza G, Venturi G. The Italian 2017 Outbreak Chikungunya Virus Belongs to an Emerging *Aedes albopictus*-Adapted Virus Cluster Introduced From the Indian Subcontinent. *Open Forum Infect Dis*. 2018 Dec 12; 6(1): ofy321.
2. Errico G, Di Pilato V, Monaco M, Giani T, Del Grosso M, Antonelli A, David S, Lindh E, Camilli R, Pantosti A, Rossolini GM. The emergence of new high-risk clones driving the changing epidemiology of carbapenemase-producing *Klebsiella pneumoniae* from invasive infections in Italy: a phenotypic and molecular survey. Manuscript in preparation.
3. Einöder-Moreno M, Carattoli A, Lindh E, Busani L, Luzzi I, Tourdjman M. et al. Typhoid Fever outbreak linked to Rainbow gathering in Northern Italy. Manuscript in preparation.
4. Giufrè M\*, Lindh E\*, Cardines R, Pezzotti P, Cerquetti M. Invasive *Haemophilus influenzae* type b (Hib) disease in children in Italy, after 20 years of routine use of conjugate Hib vaccines. Manuscript in preparation. \* equal contribution

## Reports

1. MDR TB EQA performed in 2017-2018
2. Evaluation of the enhanced surveillance system for Legionnaires' Disease
3. Invasive *Haemophilus influenzae* type b (Hib) disease cases in children in Italy, after 20 years of routine use of conjugate Hib vaccines
4. Invasive Group B streptococcal disease in infants in Italy, 2015-2018
5. Malaria – National surveillance in a non-endemic country

## Conference presentations

1. ESCAIDE 2018, November 23, oral presentation: 'Whole genome sequence analysis reveals a novel cluster of strains with a unique amino acid substitution pattern, responsible for the recent Italian-2017 and Pakistani-2016 Chikungunya virus outbreaks'
2. ESCAIDE 2019, November 27, poster presentation: 'Typhoid in the woods – implementation and impact of genomics for typing *Salmonella enterica* serovar Typhi in a National Reference Centre'

## Other presentations

1. 'Mechanisms of Carbapenem Resistance in Enterobacteriaceae', presentation for peers at Introductory course, October 2017
2. 'Application of WGS technologies for surveillance and outbreak investigations in expert laboratories in Italy', presented at ECDC in February 2018
3. 'What kind of evidence is there for infection (past and present) and immunity?' lecture and laboratory results interpretation exercise for epidemiologist at Vaccinology module, June 2019

## Other

1. Suligoï B, Salfa MC. et al. Sexually transmitted disease – information booklet for youth. Translation from Italian to English. In preparation.
2. Risk assessment form for laboratory work

## Training modules

The Introductory Course and Project review-module familiarised participants with concepts relating to communicating efficiently and presenting scientific data and on how to receive and give constructive feedback. The Management, Leadership and Communication in Public Health-module trained participants in communication to different audiences.

## 9. EPIET/EUPHEM modules attended

1. Introductory course, Spetses, Greece (three weeks, September 2017)
2. Outbreak investigation, Robert Koch Institute, Berlin, Germany (one week, December 2017)
3. Bio-risk and quality management, ECDC, Stockholm, Sweden (one week, February 2018)
4. Management, Leadership and Communication in Public Health, ECDC, Stockholm, Sweden (one week, February 2018)
5. Multivariable analysis, Nicosia, Cyprus (one week, April 2018)
6. Rapid assessment and survey methods, Athens, Greece (one week, May 2018)
7. Vaccinology, Rome, Italy (one week, June 2019)

8. Project review 2019, Prague, Czech Republic (one week, August 2019)

## 10. Other training

- International Shipment of Dangerous Substances (WHO, February 2018)
- Online courses:
  - UNDSS 'Basic Security in the Field II', certificate 11 May 2018;
  - UNDSS 'Advanced security in the Field II', certificate 13 May 2018;
  - GOARN 'Working with GOARN in the Field', certificate 17 May 2018

## Discussion

### Coordinator's conclusions

Erika Lindh undertook her fellowship at the Istituto Superiore di Sanità, where all colleagues highlighted her kindness and remarkable ability to communicate and bring together teams to develop fruitful collaborations. Erika's expertise in molecular biology and virology, enhanced by the acquisition of skills in public health microbiology during the projects readily provided by the supervisors during the fellowship saw her accomplish outputs of impressive quality. Her ability to apply genotyping methods aided important outbreak investigations in Italy. Establishing whole genome sequencing analysis pathways was a very valuable contribution from the fellow to the site. Dedicated, organised and efficient, it has always been a pleasure to discuss with Erika the scientific approach to her new projects and her progress, whilst observing her successfully navigate the complexities of balancing work and family life whilst accomplishing her fellowship objectives. At the end of her fellowship I wish Erika all success and happiness in the new and exciting next steps.

### Supervisor's conclusions

Erika has been the first EU-track EUPHEM fellow at the Infectious Disease Department of ISS.

We as supervisors and the entire Department were highly engaged by the new experience and indeed our expectations were met. Erika is a very motivated, competent and highly organized fellow. Since the beginning Erika was fully committed with the projects, constructively collaborating with the project supervisors and the staff, and contributing to the accomplishment of the studies with her expertise. We gratefully acknowledge the fellowship program that allowed that Erika's skills could contribute to the advancement of genomic expertise in the Department. At the same time, thanks to the project supervisors' engagement the Department was able to provide Erika with valuable projects adding to Erika's competencies in Public Health Microbiology.

Erika was able to manage the duties of the fellowship showing strong determination and commitment to accomplish the tasks she was in charge of. The success of the fellowship in the Department can be measured also by the sympathy and appreciation she raised among all the people she worked with in the Department.

### Personal conclusions of fellow

The fellowship has exposed me to a broad range of activities within public health. It has provided a unique opportunity to be involved in outbreak investigations and in surveillance of infectious disease, and deepened my expertise within microbiology, including bacteriology, virology and parasitology, and in intervention epidemiology. Beyond all, the two years in the program has trained me to bridge the gap between the disciplines of microbiology and epidemiology and appreciate the public health implications in different scenarios. Working with the diverse projects allowed me to work with and learn from professionals with profound expertise in microbiology and public health. A strong asset of the program is the inclusion of fellows in the international multidisciplinary network of professionals working in public health in Europe and beyond, which will nurture their professional growth for years to come.

## Acknowledgements of fellow

First, I would like to express my deep appreciation to my supervisor Annalisa Pantosti for guiding me through the fellowship with the profound wisdom that only experience may bring. A sincere thanks to Loredana Ingrosso, my co-supervisor, for your support and engagement. Patrizio Pezzotti, my EPIET supervisor, thank you for all the support that you have given me in statistical issues and for guiding me through the Italian coffee culture. I greatly appreciate the input of my front-line, Aura Andreasen, for your availability and for sharing your sound and human thoughts on work and life. A sincere thanks to Giovanni Rezza, head of the department of Infectious Disease at Istituto Superiore di Sanità, for the opportunity to work in the institution and for providing the welcoming and friendly atmosphere to work in. My warmest thanks to all the project supervisors and collaborators for giving me the opportunity to take part in your daily work and responsibilities. I truly enjoyed working with all of you.

Finally, thank you to all the EPIET/EUPHEM coordinators, heads of programme and staff of the EPIET office for making the program what it is. You've put a huge amount of heart, enthusiasm and scientific input in all the modules that you've organized. The fellows of C2017, thank you for being the best ever companions on this journey. I sincerely hope that the spirit that you carry will last till the end of our careers.