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# ON THE TRAIL OF ZOOONOTIC PATHOGENS

The use of a combination of comparative and functional genomics helps to survey, prevent and combat bacterial infections of humans and livestock, as Ulrich Dobrindt and Helge Karch discuss

One research focus at the Institute of Hygiene, University of Münster, is based on whole genome sequence information and aims at the analysis of the evolution and epidemiology of clinically relevant bacterial pathogens, as well as their virulence and resistance-related traits and zoonotic risk.

In recent years, the number of infections caused by antibiotic-resistant pathogens has drastically increased worldwide. Many of the traditional antibiotics have become ineffective in the treatment of infections in humans and animals. This is a serious problem for our healthcare system because infections caused by multidrug-resistant bacteria are difficult to treat, extend the duration of treatment, and lead to increased mortality and higher treatment costs. The development and spread of resistant human pathogens correlates with the extensive use of antibiotics in livestock production.

Enterohaemorrhagic *Escherichia coli* (EHEC) naturally colonise the intestines of ruminants and are excreted in the animal faeces. EHEC infections may be associated with a severe course of illness and lifelong disability (e.g. hypertension or renal insufficiency), and can be fatal. Accordingly, EHEC are among the most important bacterial pathogens that can be transmitted through food. Similarly, Methicillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-expressing enterobacteria are important human pathogens responsible for severe infection, but they also colonise food-producing animals, e.g. pigs, cattle or poultry. From these reservoirs they can be directly, or via the food chain, transmitted to humans and cause disease, even epidemics, thus placing a burden on human health and

veterinary systems. This negatively affects the security of food, sustainability of the food chain, as well as consumer confidence in food and food trade. 'One health' approaches are required to analyse the reservoirs, evolution, virulence and resistance traits of these zoonotic pathogens in the human and veterinary fields, including the food chain.

## DNA sequence-based approaches for surveillance of outbreaks and transmission routes of zoonotic pathogens

Next-generation sequencing (NGS) and comparative analysis of complete genomes offer a high discriminatory power for the (sub)typing of bacterial isolates. The combination of DNA sequence data and temporal-geographic or disease or phenotype information enables us to identify so far unrecognised genetic relationships. Consequently, these approaches are important for public health issues, including improved surveillance and identification of outbreaks. The availability and storage of large bacterial genome datasets in combination with other metadata allows us to rapidly identify common sources of infection and to improve our understanding of outbreaks (Fig. 1). As zoonotic pathogens are frequently spread even via long distances by vectors, which are contaminated by very low numbers of pathogens, molecular epidemiology and typing of foodborne pathogens require very sensitive and comprehensive approaches.

Using *Campylobacter* and EHEC as model systems, we generated DNA sequence-based data and combined them with clinical, microbiological, epidemiological analyses to develop tools for improved risk assessment for public health, food and animal health. Our work identified single nucleotide polymorphisms in EHEC or *Campylobacter* biomarkers (e.g. the Shiga toxin-encoding or flagellin-encoding genes), which could be correlated with host specificity, their phylogenetic background and the clinical outcome. Molecular epidemiological analyses of MRSA isolates based on *S. aureus* protein A (*spa*) typing allowed the comparison of MRSA strains associated with human infection with isolates from livestock animals, and demonstrated that livestock-associated MRSA clones can be major sources of human infection.

Under the framework of different national and international consortia, also supported by the European Community under the Seventh Framework Programme (FP7), we compare EHEC and other *E. coli* genome sequence data to identify discriminative biomarkers. Our findings contribute to improved pathogen monitoring by rapid identification and comparison of different isolates. This will also result in a better understanding of the ecology of these bacteria in their animal reservoir, their survival

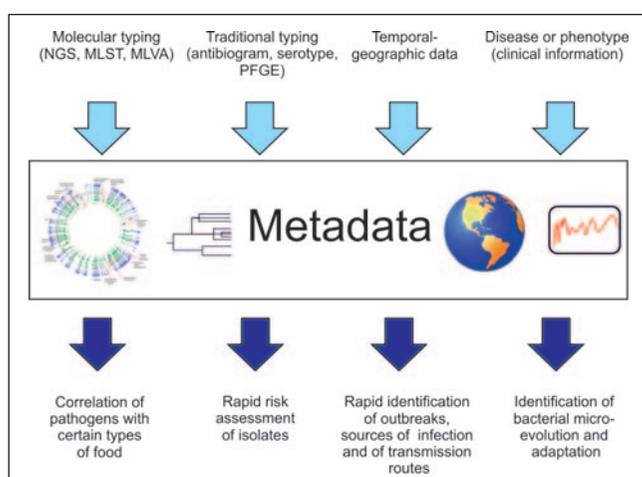


Fig. 1 NGS and comparative genomics are powerful tools for public health and food safety issues and improve the elucidation of transmission routes, the surveillance of outbreaks and the detection/risk assessment of zoonotic pathogens

and persistence in the environment, but also of their entry into the food chain and their transmission routes.

**Zoonotic pathogens: adaptation to different environmental conditions and mechanisms of host-pathogen interaction**

To increase food safety, we have to learn more about strategies of foodborne pathogens to interact with different food matrices and to survive in the environment. One of our aims supported by the FP7 RTD project ANTIGONE is to elucidate the EHEC factors critical to their survival on and interaction with plant material. NGS data facilitates the investigation of bacterial factors and genetic mechanisms involved in the emergence and evolution of highly pathogenic bacteria. We investigate bacterial traits required for host colonisation or infection. Complete genome sequence data help to identify such adaptive traits. Additionally, the heterogeneity of the genome content of individual clones, e.g. during outbreaks, contributes to improved diagnostic tools.

Besides EHEC, the zoonotic potential of avian pathogenic *E. coli* (APEC) – which cause high economic losses due to morbidity and mortality in the poultry farming industry all over Europe – is also discussed. Interestingly, APEC and *E. coli* isolates, which cause extra-intestinal infection in humans, have very similar virulence gene repertoires. APEC are discussed to serve as a reservoir for virulence and antibiotic resistance genes accessible to human pathogenic variants. Bacterial infections during livestock production are usually treated with antibiotics. However, to meet consumer demands, antibiotic use in animal production has to be reduced. This calls for the development of alternative approaches to reduce poultry colonisation by APEC.

One of our projects funded by the EMIDA ERA-Net deals with the characterisation of APEC factors, which are required for poultry

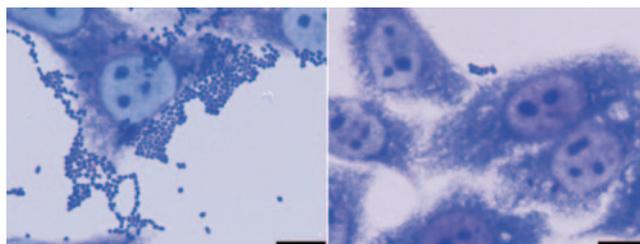


Fig. 3 Adhesion of different EHEC isolates to HEp-2 cells (scale bar = 10µm)

colonisation as well as for human infection. Genome comparison including more than 100 chicken commensal *E. coli* and APEC genomes from different European countries led to the identification of genomic regions which distinguish between commensal and pathogenic isolates. Our data demonstrate that certain important clones comprise chicken commensal *E. coli*, APEC isolates as well as multiresistant *E. coli* from human infection (Fig. 2), thus supporting a potential zoonotic risk of these bacteria. Phenotypic analysis of pathogenic *E. coli* also identified traits which may distinguish different pathogenic *E. coli* variants from commensals. To further investigate the underlying mechanisms of the differential interplay between zoonotic pathogens with their human or animal hosts, we analyse their global gene expression profiles as well as their interaction with eukaryotes (Fig. 3).

The comprehensive analysis of the epidemiology, virulence and fitness traits and adaptability of zoonotic pathogens will present us with a more complete picture of their ability to efficiently colonise different hosts. These findings promote the development of new therapeutic strategies to specifically interfere with relevant virulence or colonisation mechanisms in the animal reservoir, the food chain and the infected patient. Corresponding research activities will not only increase consumer safety and our quality of life, they will facilitate trade and strengthen the European food and agricultural sector, as well. The development of early warning systems, including the implementation of DNA sequence-based bacterial typing and risk assessment, also strengthens the idea of ‘Global Research Collaboration for Infectious Disease Preparedness’.

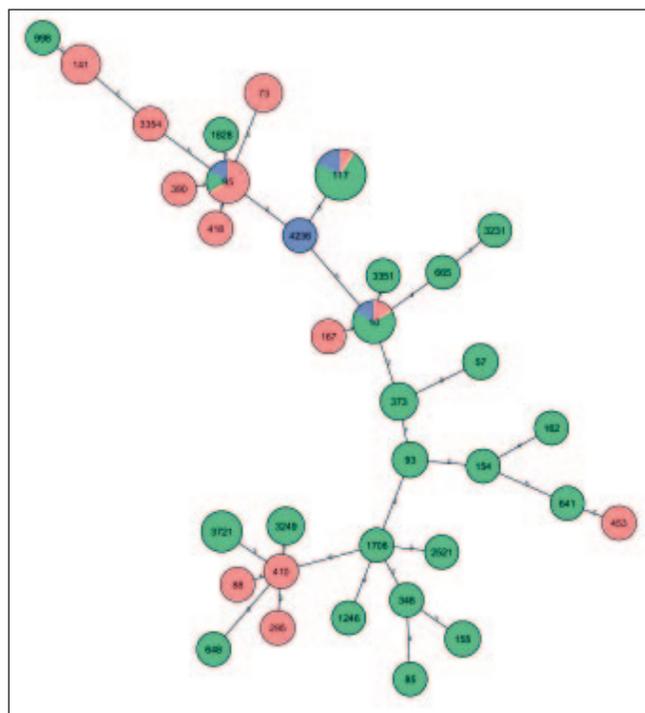
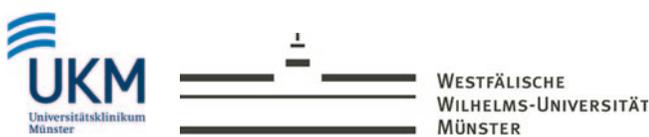


Fig. 2 Clonal analysis and distribution of chicken commensal (green), APEC (blue) and human pathogenic *E. coli* (red) isolates



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