

Investigations by the Institut Hospitalo-Universitaire Méditerranée Infection of food and food-borne infections in the Mediterranean Basin and in sub-Saharan Africa

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Abstract

Food-borne infections are major causes of public health concern in developing and developed countries. During the past decade, the Institut Hospitalo-Universitaire Méditerranée Infection has conducted or been involved in multiple investigations that aimed at identifying the sources and strains responsible for food-borne diseases and therefore at improving the understanding, diagnosis, prevention and control of these infections. Investigations were conducted in the Mediterranean area and in sub-Saharan Africa on more than 15 food-borne agents, 17 food products and 14 antibiotic resistance-associated genes. Multiple sources, including unexpected ones, and pathogens, including emerging ones, were involved. Travelling in developing countries and zoonoses are major contributors to food-borne infections, while food-borne transmission of resistance-associated genes is increasingly reported. However, risk factors and pathogens associated with food-borne infections likely remain untapped and must be more extensively investigated, monitored and regularly reassessed. Diagnostic tests based on new technologies and real-time surveillance tools based on microbiology laboratory data are promising approaches to detect known food-borne infections and decipher new ones. Studies of the microbiota and its relationships with dietary patterns are also worth being conducted.

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Keywords: Africa, bacteria, food, food-borne, fungus, IHU Méditerranée Infection, infections, Mediterranean Basin, virus, zoonosis

Original Submission: 25 February 2018; **Revised Submission:** 2 July 2018; **Accepted:** 22 August 2018

Article published online: 6 September 2018

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Introduction

Food-borne infections are major causes of public health concern in developing and developed countries and can have a considerable social and economic cost [1,2]. Nevertheless, their global burden remains insufficiently documented. These infections mostly involve bacteria, viruses and parasites that use food as vehicle for their transfer from animals to humans and can generate secondary transmissions between humans [3]. During the past decade the Institut Hospitalo-Universitaire

Méditerranée Infection has conducted or been involved in multiple investigations that aimed at identifying the sources and strains responsible for food-borne diseases and therefore at improving the understanding, diagnosis, prevention and control of these infections. We summarize here its contribution to the study of food-borne infections.

Methods

We used the following keywords, cross-matched with names from people of our institution, to search in PubMed, Google Scholar and ISI Web of Science: food, food-borne, alimentary, sausage, shellfish, meat, fish, fruit, vegetable, dairy product or sauce; and infectious, infection, bacteria, virus, parasite, microorganism, microbe, microbiology, virology, parasitology or mycology.

Bacteria

As emphasized by the example of the German outbreak due to *Escherichia coli* O104:H4 [4], food-borne bacterial infections can be due to the presence of bacterial toxins in food. Alternatively, they can result from the presence of pathogenic bacteria in food products. In our experience, such infections have been suspected several times. In 2015, our laboratory data-based surveillance system, PACASurvE (Provence-Alpes-Côte d'Azur Surveillance Epidemiologic System) [5], detected several consecutive abnormal increases in the number of *Enterococcus faecalis* infections, especially community-acquired urinary tract infections, in different areas of the Provence-Alpes-Côte d'Azur French region [6]. Investigations led us to strongly suspect a zoonotic origin for the outbreak, with chicken-based food as a vehicle for the pathogen. Another example is that of *Enterococcus cecorum*, a bacterium rarely involved in human infections but normally present in the intestinal tract of domestic animals, which we identified in two patients receiving immunosuppressive drug regimens hospitalized in Marseille public hospitals [7]. In this case, we finally hypothesized that the two infections originated from food-mediated acquisition of the bacteria facilitated by immunosuppression. Similarly, in 2016, we were the first to identify *Vagococcus lutrae*, a bacterium initially described in the common otter as a possible human pathogen, in a hospitalized patient [8]. In this case we also hypothesized that bacterial infection was food-borne, especially through consumption of seafood products and possibly promoted by poor hygiene. In another two studies investigating the epidemiology of *Coxiella burnetii*, the zoonotic agent of Q fever, among children hospitalized in a tertiary-care paediatric hospital in Athens, Greece, and a *C. burnetii* outbreak in Southern France, we clearly identified the role of cheese and unpasteurized dairy products in human infections [9,10]. *Coxiella burnetii* DNA, but not viable bacteria, was also described in dairy products in France [11].

Fortunately, all food-borne bacteria do not cause diseases in humans. Most of the time, these bacteria colonize the human gut without any detrimental impact to the host. Thus, yoghurts and probiotic food are major sources of living bacteria [12]. Intriguingly, some of our works on food also allowed us to identify new bacterial species in daily food products. Indeed, we were the first to identify *Gracilibacillus massiliensis* sp. nov., a moderately halophilic Gram-positive bacterium in commercial table salt originating from the saline of Aigues-Mortes, Southern France [13]. Moreover, we identified in fermented cow's milk products from Algeria a new strain of *Lactococcus garvieae*, a bacterial species commonly used in the manufacture of fermented milk products and meats [14]. Also, a study conducted

among 331 pilgrims departing from France to the 2011 Hajj revealed that 8% of them had previously drunk camel milk, most often in North Africa and Saudi Arabia; such milk has been involved in several zoonotic infections in humans, including brucellosis [15].

Antibiotic resistance genes and antibiotic-resistant bacteria

Antibiotic resistance genes and antibiotic-resistant bacteria in food-producing animals and vegetables

Our institute proved that food products and food-producing animals from the Mediterranean Basin are reservoirs for antibiotic resistance genes (ARGs) and antibiotic-resistant bacteria (ARB) (Fig. 1). Indeed, in Algeria and Lebanon, we identified chicken, cattle and pigs as possible reservoirs for CTX-M, SHV, TEM, CMY, VIM, OXA-23, OXA-58, *aadA*, *qnrA*, *qnrB* and *mcr-1* producing bacteria [16–22]. Moreover, our work performed in Béjaïa, Algeria, allowed us to isolate from tomato, lettuce and parsley freshly purchased in markets three *Klebsiella pneumoniae* strains harbouring an OXA-48 carbapenemase [23].

ARGs and ARB transmitted by food to humans

Some of our works on food and food-producing animals in the Mediterranean Basin led us to suspect food-mediated transmission of ARB that led to human infections. In a recent work, we identified that seven extended spectrum β -lactamase-producing *Salmonella* serotype Heidelberg detected in broiler chickens (five strains) and hospitalized humans (two strains) from Northeastern Algeria belonged to the same sequence type (ST15), suggesting a possible food-borne transmission of this strain between chicken and humans through the food chain [20]. However, as mentioned above, not all food-borne bacteria are responsible for diseases in humans. In these cases, ARGs and ARB can be asymptotically acquired by humans through food consumption [24]. In our institute, asymptomatic food-borne acquisition of ARGs and ARB are particularly studied in pilgrims returning from the Hajj. In these populations, studies of the gut and pharyngeal carriage of ARB and ARGs in pilgrims before, during and after the Hajj enabled us to identify an increase in asymptomatic carriage of some ARGs and ARB during and after this pilgrimage, including *bla*_{OXA-51-like} *Acinetobacter baumannii* and plasmid-mediated *mcr-1* and New Delhi metallo- β -lactamase 5 ARGs [25]. These observations, coupled with the fact that some pilgrims carried the same ARB clones after returning from the Hajj [25], led us to suspect food as the main common reservoir of the ARG/ARB.



FIG. 1. Countries from Mediterranean Basin, Africa and Middle East where identifications of food-borne pathogens in food and/or humans involved teams from Institut Hospitalo-Universitaire Méditerranée Infection. Virus, bacteria and antibiotic schematics indicate that viruses, bacteria and/or antibiotic-resistant bacteria/genes have been identified in food (food item schematic) and/or in asymptomatic carriers (green-person schematic) and/or in diseased patients (red-person schematic). The food item schematic represents some examples of food items that may be involved in transmission of infectious agents, but they are not necessarily those involved or suspected for a given geographical area/country.

Parasites and fungi

Toxoplasma gondii-specific immunoglobulin G was found in the Var Department, Southeastern France, in 17% of muscle extract samples collected from 841 wild boars [26]. This indicates that consumption of raw or undercooked meat from wild boars is an important risk factor for infection with *T. gondii*. In addition, a total of 18 fungal species from the *Ascomycota*, *Basidiomycota* and *Chytridiomycota* phyla were detected in faeces collected from a 27-year-old white woman living in Marseille, France (16 by culture, seven by PCR), and many of these fungal species, for which the clinical significance of their presence in the human gut is unknown, may originate in food [27]. Eight fungi (*Aspergillus flavipes*, *Beauveria bassiana*, *Isaria farinosa*, *Penicillium brevicompactum*, *Penicillium dipodomyicola*, *Penicillium camemberti*, *Climacocystis* sp. and *Malassezia restricta*) were indeed found for the first time in human gut microbiota.

Viruses

Hepatitis E virus

During the past decade, research has revealed that hepatitis E virus (HEV) has a porcine reservoir and has caused food-borne autochthonous acute hepatitis. In France, we were the first to describe in 2009 the presence of this virus in two thirds of the pigs from a farm located in southeastern France [28]. Then in 2010 we linked HEV infection to consumption of pig liver sausage, which are often consumed uncooked [29]. This was largely confirmed afterward [30,31]. Consumption of pig liver sausage purchased in southeastern France was linked to hepatitis E in Italy [32]. In southeastern France, consumption of pig liver sausage was documented in approximately half of the HEV infections [33]. We showed the stability of HEV prevalence among farm pigs and the emergence in France of new genotypes in these pigs and concurrently in humans [34]. Although HEV is

mostly documented as involved in likely waterborne outbreaks in sub-Saharan Africa, we also detected HEV in farm pigs in this geographical area [35]. Concurrent with being revealed as having an extensive porcine reservoir, HEV was reported to cause acute liver failure and death [36,37]. Furthermore, HEV was shown to be capable of determining chronic hepatitis in solid organ transplant recipients [38,39]. We found it to be associated with cirrhosis [39], and it was thereafter confirmed that HEV could cause cirrhosis as soon as 2 years after infection [40]. Recently we described a case of hepatocellular carcinoma in a cirrhotic patient with chronic hepatitis E [41]. Furthermore, HEV infections have been increasingly linked to neurological disorders [42,43].

Plant viruses

Although animal/human infections and vegetal infections are distinct fields, there are hints that plants and animals can be infected by the same, or at least similar, infectious agents. Plant-associated bacteria and viruses have been found in the gut. Notably, tobamoviruses were the most abundant RNA viruses in human stool in one metagenomic study [44]. We further identified pepper mild mottle virus (PMMoV) in 7% of the stool samples from 304 adult patients from Marseille University hospitals; the presence of this virus was associated with fever, abdominal pain and pruritus [45]. Concomitantly, we found that 57% of pepper samples or pepper-derived food products were positive for PMMoV RNA, and PMMoV load was dramatically high in Tabasco sauce. We then detected tobacco mosaic virus in 100% of tobacco cigarettes and in the saliva of 45% of smokers [46]. These findings, as well as those from other studies, question whether plant viruses from food are only transient passengers in humans, or whether they could interact with them [47].

Giant viruses

Mimiviruses, which are giant viruses of amoebae first described in 2003 in our laboratory, were recently found in oysters from Brazil [48,49]. These mimiviruses, which are common in water and soil worldwide, have been suspected to cause pneumonia and were isolated from bronchoalveolar fluid and stools from patients with pneumonia [50,51].

Conclusion

Food-borne infections appear to involve multiple sources and agents, and can be unpredictable in some cases. They require researchers to conduct investigations to decipher or confirm their sources and modes of transmission. Travel abroad is

highly involved in the transfer of pathogens from one geographical area to another [52]. This is well exemplified by investigations conducted on the carriage and transmission of bacteria and viruses promoted by mass gatherings such as the Hajj [25], and it warrants collaborations between countries on both sides of the Mediterranean Sea, such as those (REMEDIER, GIRAFE) involving our institute.

Zoonoses are other major contributors to food-borne infections. Animal-derived products potentially harbouring various bacteria and viruses can also travel from one continent to another, as recently exemplified in our laboratory using metagenomics for African simian bushmeat seized at a French airport [53]. Thus, in this study, metagenomic sequencing of the DNA and RNA viromes detected sequences related to bacteriophages from families *Siphoviridae* and *Myoviridae* that can infect bacteria potentially pathogenic for humans such as *Bacillus* spp., *Enterococcus* spp. or *Staphylococcus* spp. Many sequences related to DNA from parasites such as *Spirometra erinaceiropaei*, a tapeworm pathogenic for humans, were also identified. In addition, food-borne transmission of resistance-associated genes is increasingly reported.

Taken together, previous findings suggest that risk factors and pathogens associated with food-borne infections remain largely untapped and must be more extensively investigated, monitored and regularly reassessed. Furthermore, they warrant the implementation of new technology-based diagnostic tests, approaches and strategies [12,54,55], including culturomics, proteomics and genomics, to detect known infectious agents and discover new ones. Moreover, real-time surveillance tools, including some based on microbiology laboratory data such as those set up by our institution in southeastern France and in sub-Saharan Africa, deserve implementation [5,56]. Finally, the exploration of the microbiota and its relationships with dietary patterns is another important research field being explored at the Institut Hospitalo-Universitaire Méditerranée Infection [57,58].

Acknowledgements

Supported in part by the French government under the 'Investissements d'avenir' (Investments for the Future) programme managed by the Agence Nationale de la Recherche (Méditerranée Infection 10-IAHU-03).

Conflict of interest

None declared.

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