In September 2013, leptospirosis was diagnosed in two Spanish travellers returning from Thailand. The first case walked in floodwater in the Phi Phi Islands in pouring rain: 20 days later he presented with fever and acute hepatitis. The second presented with fever and renal failure 17 days after visiting the islands. These cases remind clinicians to consider leptospirosis in febrile patients with a history of contact with flood or fresh water while travelling to tropical countries.

Of the over 1,400 species of infectious organisms known to be pathogenic to humans, 60% are zoonotic, i.e. transmissible from animals to humans [1]. We therefore continuously face the threat of newly emerging pathogens with a major health impact. In the last decade, viral zoonoses have resulted in numerous human cases of infection with e.g. influenza A viruses, Ebola virus, Nipah virus, Hendra virus, severe acute respiratory syndrome (SARS) coronavirus, and Middle-East

**Figure**

Wild aquatic birds and bats are thought to be the reservoir for many virus families in nature

HMPV: human metapneumovirus; MERS: Middle-East respiratory syndrome; PIV: parainfluenza virus; RSV: respiratory syncytial virus; SARS: severe acute respiratory syndrome.

Blue: influenza viruses, red: paramyxoviruses, green: coronaviruses. Dotted arrow: The presence of influenza viruses in both species suggests that transmission from birds to bats, or the other way around, may have occurred in the past.

As humans do not frequently come into contact with bats and wild birds, they are more likely to contract zoonotic viruses via intermediate hosts such as domestic birds and mammals. Such zoonotic events almost always result in isolated cases of human infection, as indicated under ‘zoonosis’. Rarely, upon mutation or reassortment, these zoonotic viruses adapt to the new human host, acquire human-to-human transmissibility, and may start a pandemic (as depicted under ‘pandemic’). In the last century alone, four human influenza pandemics have occurred. Pandemics of paramyxoviruses and coronaviruses are even more rare, yet numerous viruses of animal origin that belong to these families are also endemic in humans.
Wildlife can host an enormous diversity of viruses, which generally do not cause severe disease in these reservoir hosts. Bats have been recognised as reservoir hosts of viruses of the Filoviridae, Paramyxoviridae, and Coronaviridae families [2,3], while wild birds harbour the greatest diversity of influenza A viruses. Recently, close relatives of avian influenza A virus were also found in bats [4]. Occasionally, viruses are transmitted from their reservoir hosts to other animal species, intermediate hosts, from which the viruses may subsequently be more efficiently transmitted to humans, e.g. as a consequence of more frequent contact. Unfortunately, very little is known about the genetic and phenotypic viral and host traits that facilitate interspecies transmission. In addition, knowledge on the mechanisms by which these zoonotic viruses may subsequently adapt to efficient replication and spread in humans is lacking. Recently, progress has been made towards understanding the genetic and phenotypic requirements of avian influenza viruses to become transmissible in ferrets [5-9].

Influenza A viruses are among the most intensively studied viruses when it comes to host range and transmission. The reason is that influenza A virus zoonoses and pandemics occur relatively frequently compared with other virus families. Influenza A viruses have been isolated from many hosts, but wild birds in the orders Anseriformes (ducks, geese and swans) and Charadriiformes (gulls, terns and waders) as well as bats are thought to form the virus reservoirs in nature (Figure). At least 18 subtypes of the influenza virus surface glycoprotein haemagglutinin (HA or H) and 11 subtypes of neuraminidase (NA or N) have been detected in the reservoirs [4]. In the last century, only influenza A viruses of subtypes H1N1 (in 1918 and 2009), H2N2 (1957), and H3N2 (1968) have spilled over from wild birds to poultry or pigs and subsequently triggered a pandemic, with or without the requirement for prior host adaptation or reassortment (i.e. genetic mixing of gene segments). However, avian influenza viruses circulating in poultry (e.g. of subtypes H5, H6, H7, H9, and H10) have occasionally crossed the species barrier to infect humans, raising concerns of a new pandemic threat. The continuing circulation of highly pathogenic avian influenza (HPAI) H5N1 viruses in poultry in Asia and the Middle East has resulted in hundreds of millions of poultry deaths. Cross-species transmission events of H5N1 virus have been reported for several species of wild birds and mammals, including humans (Figure). However, sustained human-to-human transmission has not yet been described.

A study that appears in the current issue of Eurosurveillance by Chea and colleagues investigated two cases of human influenza A(H5N1) virus infection in Cambodia [10]. After the post-mortem diagnosis of influenza A(H5N1) virus infection in a mother and her child, the authors performed a follow-up study of individuals who had been in contact with the two cases. The mother and child were assumed to have been infected from a common poultry source. Although there were no poultry samples available for retrospective laboratory confirmation of H5N1 virus infection, poultry in and around the household had started to die before disease onset of the cases. Respiratory specimens from all contact cases tested negative by RT-PCR for influenza A(H5N1) virus, and no H5N1 antibodies were detected in follow-up sera of contacts. Based on this extensive epidemiological investigation, there was no evidence of human-to-human transmission between the cases or their contacts. The authors conclude that the two cases were most probably exposed to a common source of contaminated environment.

Similar clinical, virological, and epidemiological investigations were performed by Xiao et al. [11] and Hu et al. [12], but for laboratory-confirmed cases of infection with influenza A(H7N9) virus. Since the emergence of the H7N9 virus in February 2013, only one possible human-to-human transmission event had been described [13]. Here, Xiao and colleagues describe the probable transmission of H7N9 virus from a father to his five year-old child after he worked on a wet market contaminated with H7N9 virus [11]. Disease onset in the child was 10 days later than in the father, and virus was detected in the child several days later as well. The child reportedly did not have contact with poultry in the 12 days before onset of the disease. Investigations of 40 close contacts did not result in the detection of additional cases of infection. Hu et al. describe a similar case of human-to-human transmission from a woman who also contracted influenza A(H7N9) virus at a contaminated wet market and probably transmitted the virus to her husband [12]. The man reportedly never visited wet markets and had not purchased or eaten poultry in the two weeks before the onset of his illness. Onset of disease and detection of the virus in the man occurred approximately one week later than in his wife. Again, 27 close contacts were followed up, but they all turned out to be H7N9-negative. These studies thus present two probable cases of human-to-human transmission of H7N9 virus. In both studies, high nucleotide sequence identity between the viruses from the linked patients was in agreement with this assumption. In the first study, the virus could further be linked...
Qi et al. describe the potential origin and genetic diversity of the most recently identified zoonotic influenza virus subtype, H10N8, which was detected in a patient that visited a poultry market a few days before onset of illness [19]. Phylogenetic analysis of the viruses isolated from the patient and the poultry market showed that six genes had the same genetic origin, but the PB1 and PB2 genes (that are part of the viral polymerase complex) were of a different origin. These two genes from the human and chicken virus may be derived from H9N2 chicken and H7 duck influenza viruses, respectively. The genetic differences between the internal genes of the human and chicken viruses suggest that H10N8 viruses continue to undergo reassortment, as reported previously for H7N9 virus. The authors suggest that the H10N8 viruses have become established in poultry and speculate that the diversity of the H10N8 viruses may be much higher than reported so far.

Interestingly, the PB2 gene of the human H10N8 virus contained an E627K mutation, which is a well-known mammalian adaptation mutation associated with virulence and transmission of influenza viruses in mammals, and which was absent in the avian H10N8 strain. This same mutation was also noted in a fifth mammalian adaptation mutation associated with transmission between family members.

The five publications in the current issue of *Eurosurveillance* on the potential transmissibility and evolution of influenza viruses highlight the impact of these zoonotic viruses on global health. Surprisingly little is known about the routes and mechanisms of virus transmission. As a consequence of these knowledge gaps, key questions in public health such as “Can newly emerging viruses acquire the ability of human-to-human transmission to trigger a pandemic?” remain unanswered. Increased knowledge is important to predict risks and to adapt pharmaceutical and non-pharmaceutical intervention strategies to prevent outbreaks or pandemics. Currently, we appear to rely on humans as sentinels for virus outbreaks in animals and often apply a reactive rather than pro-active approach to limit the impact of emerging virus infections. Implementation of the One Health concept as an approach to overcome some of the difficulties, including efforts to improve laboratory capacity and surveillance systems in humans and animals, may limit the impact of zoonotic and pandemic threats in the future.

Conflict of interest
None declared

Authors’ contributions
Sander Herfst and Ron Fouchier wrote the manuscript.
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