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Factors determining human-to-human transmissibility of zoonotic pathogens via contact

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The pandemic potential of zoonotic pathogens lies in their ability to become efficiently transmissible amongst humans. Here, we focus on contact-transmitted pathogens and discuss the factors, at the pathogen, host and environmental levels that promote or hinder their human-to-human transmissibility via the following modes of contact transmission: skin contact, sexual contact, respiratory contact and multiple route contact. Factors common to several modes of transmission were immune evasion, high viral load, low infectious dose, crowding, promiscuity, and co-infections; other factors were specific for a pathogen or mode of contact transmission. The identification of such factors will lead to a better understanding of the requirements for human-to-human spread of pathogens, as well as improving risk assessment of newly emerging pathogens.

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Introduction

Infectious diseases are the second leading cause of death worldwide after cardiovascular diseases [1]. More than half of the known pathogens that are able to infect humans are of zoonotic origin [2]. Once a zoonotic pathogen has crossed the species barrier by infecting humans, its success in the human population will depend on whether or not it can acquire the ability of sustained human-to-human (H2H) transmissibility. A better understanding of the factors that determine this ability would help to prevent the emergence or re-emergence of infectious diseases in the human population.

Transmission of infectious pathogens amongst humans can occur via multiple routes: airborne (aerosols and respiratory droplets) route, faecal-oral route, contact route or vector-borne route. In this review, we focused on pathogens that are transmitted via direct or indirect contact as their main or substantial routes of transmission. Pathogens that are mainly transmitted via the faecal-oral and food-borne routes — which also are types of contact transmission — were excluded because they are discussed elsewhere in this issue. Direct contact transmission requires physical contact between an infected person and a susceptible person and the transfer of pathogens via touching, sexual contact, or contact with bodily fluids or lesions. Indirect contact refers to the infection of a susceptible person via a contaminated surface. We divided contact transmission into four modes: skin, sexual, respiratory and multiple. We used the following examples to illustrate these four modes of contact transmission: *Treponema pallidum pertenue* (TPE) for skin contact transmission, human immunodeficiency virus type 1 (HIV-1) for sexual contact transmission, coronaviruses (CoV) for respiratory contact transmission and Ebola virus for contact transmission via multiple routes. For each of these pathogens and their specific mode of transmission, we identified the factors, at the level of the pathogen, host or environment that promoted or hindered their ability of sustained H2H transmissibility.

Skin contact transmission

The spirochete bacterium *Treponema pallidum* (ssp. *pertenue*; TPE) causes yaws. Another subspecies (ssp. *pallidum*) that causes syphilis is not further discussed here. Yaws primarily affects the skin, bones and cartilages of children in hot and humid areas of Africa and Asia and the

Pacific region. The main sources of infection are direct contact with skin ulcers.

Although TPE is traditionally considered to exclusively infect humans, it has recently been identified in African nonhuman primates. The fact that human and simian TPE strains share a high degree of genetic and functional similarity suggests that African nonhuman primates may serve as a reservoir for human infection and highlights the potential for zoonotic transmission [3].

TPE has obviously acquired the ability of sustained H2H transmissibility. There are several pathogen factors that may contribute to this ability. The spirochete evades the immune response by antigenic variation and abrogation of opsonizing antibodies [4–6], allowing it to survive permanently in the infected host. It reaches high loads in skin ulcers and the infectious dose is low. Besides entering a new host via cuts or abrasions, the closely related *T. pallidum pallidum* is known to use peptides of the outer membrane to attach to host surface proteins [7] and is reported to penetrate healthy mucous membranes [8]. Host factors favouring TPE transmission include crowded living conditions. High humidity and temperature are environmental factors that increase TPE survival outside the host. Finally, lack of surveillance and inadequate health care favour the persistence and spread of human yaws in affected countries.

Sexual transmission

The retrovirus HIV-1 is the archetypal example of a sexually transmitted human pathogen. Although HIV-1 can be contracted by sexual, percutaneous and perinatal routes, nearly 70% of infections worldwide result from heterosexual intercourse [9]. HIV-1 is the causative agent of Acquired Immune Deficiency Syndrome (AIDS) in humans, characterised by severe depletion of memory CD4+ T-lymphocytes early following infection, leading ultimately to immunodeficiency and death due to opportunistic infections and rare diseases [10]. Sexual transmission involves the transfer of virus particles or infected cells present in contaminated genital secretions or blood from an infected person to the mucosa of a susceptible host [11•]. Following transmission, the successfully transmitted founder virus population is established in CD4+ cells in mucosa/submucosa, draining lymphatics, gut-associated lymphoid tissue and systemic lymphatic tissues. Viraemia follows and increases exponentially as a result of massive virus replication in gut associated and other peripheral lymphoid tissue [11•].

HIV-1 likely originated from nonhuman primates at some time in the twentieth century. The most genetically similar and related primate lentivirus described to date is the simian immunodeficiency virus (SIV) found in chimpanzees in central Africa (SIVcpz) [12]. The majority of nonhuman primate species appear afflicted with a single strain of SIV that is mostly non-pathogenic in its natural host.

Important restriction factors by which infected hosts control lentiviral infection are tetherin [13], APOBEC3G [14] and TRIM5α [15]. The ability of the most prevalent strain of HIV-1, the M strain, to overcome such restriction factors is believed to have been critical to establish an infection in humans and to allow sustained H2H transmission, leading to the current global pandemic [16]. In comparison, the reduced abilities of other HIV-1 strains (N, O and P) and HIV-2 to counteract these restriction factors [17–19] may partly explain why they were not able to spread so effectively within the human population. Other pathogen factors that have contributed to the 'success' of HIV-1 M strain as a human pathogen, despite its relatively low infectivity (risk estimate of 1 in 1000 exposures for heterosexual transmission; [9]), include its extraordinary propensity to evolve its genome through recombination and low-fidelity replication, allowing immune and therapeutic escape [20], the nature of its long, 'latent', often sub-clinical infection, during which patients can transmit the virus [21], and high viral load. Host factors that favour transmission are the presence of other sexually transmitted diseases [9], as well as promiscuous sexual behaviour.

Respiratory contact transmission

Of the six known human (CoV), severe acute respiratory syndrome CoV (SARS-CoV) [22] and Middle East respiratory syndrome CoV (MERS-CoV) [23] are responsible for high morbidity and mortality in infected individuals. The other four human CoV (HCoV-229E, NL63, OC43, HKU1) have low pathogenicity and are associated with seasonal common colds [24].

The zoonotic origin of four out of six human CoV has been elucidated. HCoV-229E, SARS-CoV and MERS-CoV originate from bats and HCoV-OC43 from bovids, whereas animal ancestors for HCoV-HKU1 and NL63 are still to be found [25•]. The common cold CoV likely emerged a long time ago in the human population, as reflected by a global distribution and a high prevalence in humans [26]. In contrast, intermediate host species such as Himalayan palm civets [27] and dromedaries [28••] likely played a role in the recent introduction of SARS-CoV and MERS-CoV, respectively, in the human population.

SARS-CoV and MERS-CoV are predominantly transmitted via direct H2H contact, droplets and fomites [29–31], and have not (yet) established long-term and sustained H2H transmission. Virus replication occurs mainly in the lower respiratory tract (LRT) in type II pneumocytes and alveolar macrophages [32,33••,34]. Replication in the LRT may be explained by the protein expression profile of the respective receptors, the exopeptidases angiotensin-converting

enzyme 2 (ACE2) in case of SARS-CoV [35] and dipeptidyl peptidase 4 (DPP4) for MERS-CoV [36,37]. In addition, antiviral immunity of the epithelium may reduce viral replication in the upper respiratory tract (URT) [38]. For contact transmission of SARS-CoV and MERS-CoV between humans, the quantity of infectious particles seems to be an important factor as high viral loads in patients facilitated H2H transmission [39,40]. Pronounced stability of infectious CoV on surfaces for up to several days [41] could also explain fomite-related transmissions, a phenomenon that may contribute to superspreading events [39,42].

In contrast to SARS-CoV and MERS-CoV, the four common cold CoV are predominantly droplet-transmitted [43] and efficiently H2H transmissible. Virus replication occurs mainly in the central and upper parts of the respiratory tract. For HCoV-229E, this may be explained in part by the abundant expression of its entry receptor, aminopeptidase N), on non-ciliated cells of the bronchial epithelium [44]. However, although HCoV-NL63 uses the same entry receptor as SARS-CoV (ACE2) [45], it replicates mainly in the URT, perhaps because it uses additional attachment factors like heparan sulfate proteoglycans [46], or because of other as yet unknown viral replication-related or immune-related factors.

Comparison of these two groups of CoV suggests that URT replication and droplet transmission (common cold CoV) is more advantageous for sustainable H2H transmission than LRT replication and direct contact transmission (SARS-CoV and MERS-CoV). Replication in the URT, as well as transmission via the respiratory route, are also factors that favour the efficient H2H transmission of human influenza viruses, as compared to zoonotic avian influenza viruses [47].

In conclusion, high expression levels of a suitable receptor molecule in the URT combined with efficient and probably well-balanced viral countermeasures against local immunity may be major pathogen factors for zoonotic CoV to attain successful and sustained H2H transmission, as exemplified by the common cold CoV.

Multiroute transmission

Of the five known Ebola virus species, four are known to cause disease in humans [48]. Infection with Ebola virus causes Ebola virus disease (EVD), which is an acute systemic illness with a high case fatality rate [49].

Of all potential transmission routes, direct contact with patients or bodily fluids from these patients, as well as contact with contaminated surfaces or materials, is considered the most important [50,51]. Ebola virus has indeed been isolated from several bodily fluids such as blood, breast milk and semen of infected patients. In addition, Ebola virus RNA has been detected in sweat, tears, stool, on skin and from vaginal and rectal samples [52]. During the 2014 outbreak, several researchers speculated about the potential for airborne transmission of Ebola virus [53]. However, the majority of EVD patients in previous outbreaks were infected by contact transmission and all EVD outbreaks, including the 2014 epidemic, have been contained without measures against airborne transmission in the general population. This suggests that extensive airborne transmission is unlikely and of limited epidemiological importance. The 2014 EVD outbreak revealed the potential for Ebola virus to be sexually transmitted. Infectious virus and Ebola virus RNA have been detected in semen from male EVD survivors as long as 70 and 270 days, respectively, after recovery from the initial infection [54•]. This detection of infectious Ebola virus and viral RNA months after recovery from EVD highlights the potential for Ebola virus to seed new outbreaks after patients with clinical EVD are no longer present and an area is declared Ebola virus free.

The putative animal reservoirs for Ebola viruses are bats, and zoonotic transmission is thought to occur either by direct contact with bats, or via indirect transmission by contact with bats, or via indirect transmission by contact with other infected wildlife species, such as gorillas, chimpanzees or duikers, which — like humans — are affected by Ebola virus [55].

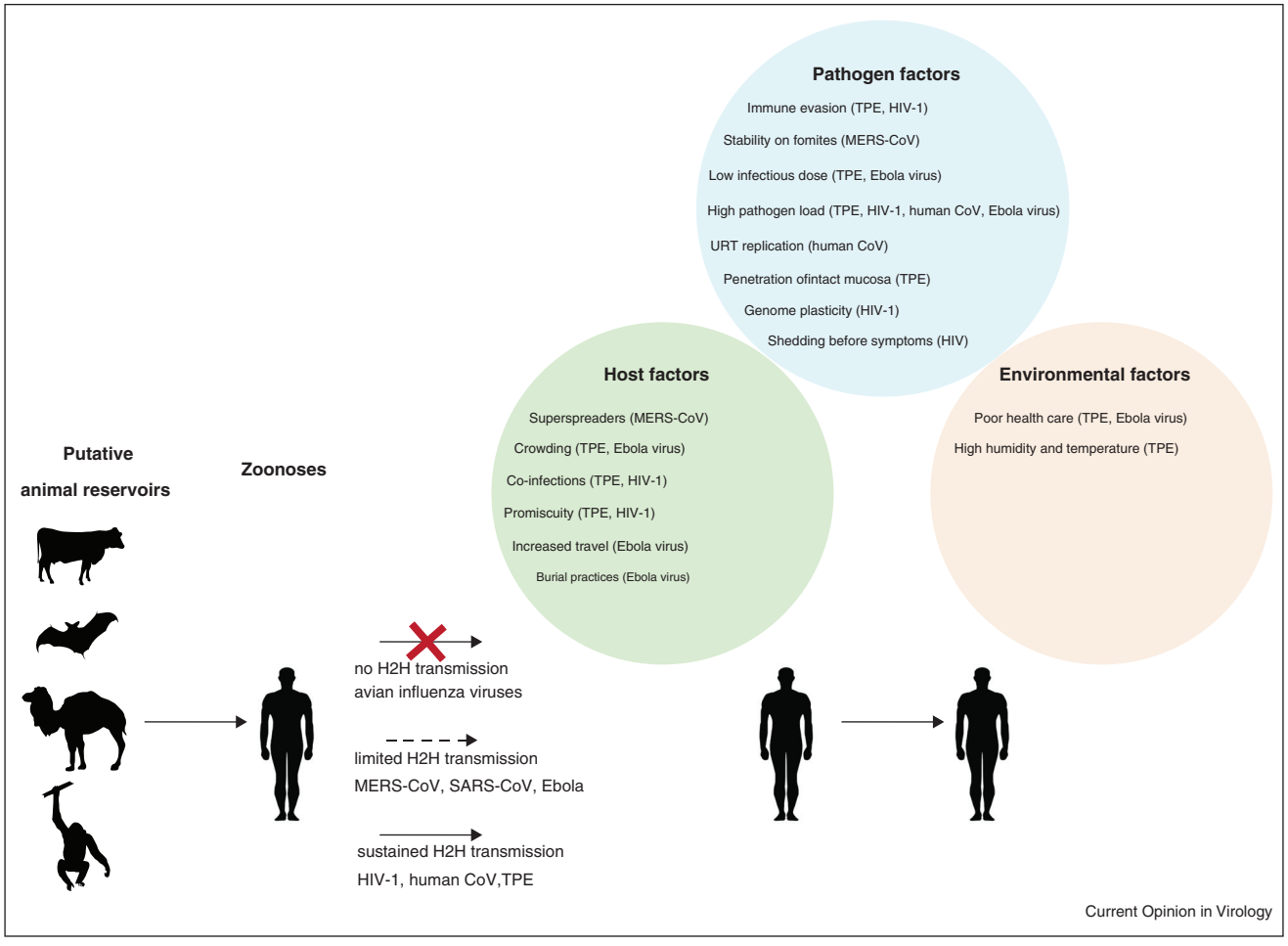
Amongst the pathogen factors that promote H2H transmission of Ebola virus is the high virus load in secreted bodily fluids combined with a very low infectious dose, as low as 10 plaque forming units as measured in experimental infection studies in nonhuman primates [56]. Amongst host factors, ancestral funeral and burial practices of deceased EVD patients, in which levels of Ebola virus remain high after death, have been identified as a major source of human infection [57]. Moreover, the 2014 outbreak of EVD in West Africa, caused by the Zaire Ebola virus, has shown, for the first time, the ability of Ebola virus to cause a long-term large-scale epidemic with sustained H2H transmission [58••]. In addition to EVD cases in Guinea, Sierra Leone and Liberia, travel-associated cases with subsequent nosocomial transmission have been reported in Mali, Nigeria and the United States. The 2014 Ebola virus strains were relatively closely related to viral strains from the previous two Zaire Ebola virus outbreaks in Democratic Republic of Congo, and, although the evolution rate of the genome of the Ebola virus during the 2014 outbreak was higher than the between-outbreak rate, the virus did not change substantially [58••,59••]. The clinical course, for example, incubation time, symptoms and development of the disease, as well as the transmissibility of the virus (R_0, basic reproductive number) were not different from those in past outbreaks of Ebola virus. Most likely, the unprecedented epidemic of Ebola in 2014 was the result of a combination of human behavioural and societal factors [60]. Firstly, West African countries never had

experienced an EVD outbreak before, other than a single case of Taï Forest ebolavirus infection in the 1980s in Ivory Coast. In addition, Guinea, Sierra Leone and Liberia are amongst the poorest countries in the world, with impaired public health infrastructures. Moreover, compared to previous outbreaks of Ebola virus, the virus was not confined to remote and rural areas and the outbreak spread into large population centres, such as Monrovia, Conakry and Freetown. The spatial connectivity provided by roads and a travelling population allowed for the rapid dissemination of Ebola virus over these three countries, before a targeted international response was initiated.

Concluding remarks

Despite being categorised under one heading, contact-transmitted pathogens may differ substantially in their specific modes of transmission: via skin, via genital mucosa, via respiratory mucosa, or via several of these modes. Nonetheless, several factors were identified that were common amongst at least two modes of transmission. Therefore, it is important to identify both factors promoting H2H transmission that are common amongst contact-transmitted pathogens and factors that are specific for each mode of contact transmission (Figure 1). Common pathogen factors were immune evasion, high viral load, and low infectious dose. Common host factors were

Figure 1



Factors, at the pathogen, host and environmental levels, that promote human-to-human contact transmission of human pathogens of zoonotic or putative zoonotic origin. The transmissibility of pathogens of zoonotic origin determines their pandemic potential. Common factors, as well as specific factors, that promoted the transmissibility via contact amongst humans of the following pathogens via the following routes are described and categorised under pathogen, host and environmental factors: *Treponema pallidum pertenue* for skin contact transmission, human immunodeficiency virus type 1 for sexual contact transmission, coronaviruses for respiratory contact transmission and Ebola virus for contact transmission via multiple routes. The pathogen to which these factors refer is indicated between brackets. *Abbreviations*: H2H: human-to-human; TPE: *Treponema pallidum pertenue;* CoV: coronavirus; MERS-CoV: Middle East respiratory syndrome CoV; SARS-CoV: severe acute respiratory syndrome CoV; HIV-1: human immunodeficiency virus type 1.

crowding, promiscuity, and co-infections. Other factors were specific to one of the modes of transmission and the pathogen described. Specific factors that may be critical for efficient H2H transmission are high viral load in skin lesions for skin contact transmission, promiscuous sexual behaviour for sexual contact transmission, URT replication and a switch from contact to aerosol transmission for respiratory contact transmission and burial practices for the transmission of Ebola virus. Identification of these factors is critical to assess the risk of contact-transmitted zoonotic pathogens gaining efficient H2H transmissibility, and to implement mitigation measures and large scale prevention campaigns in case of outbreaks.

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