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Keynote lectures

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Session: Virology and viral diseases

Lecture: **Emerging viral diseases: recent global threats**

Biosketch

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Abstract

EMERGING VIRAL DISEASES: RECENT GLOBAL THREATS

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ABSTRACT: Emerging diseases continue to arise in nature and affect living beings on all continents. A pathogenic agent is assumed to emerge worldwide every four months; 75% are zoonotic. Zoonotic diseases affect billions of people worldwide, causing millions of deaths every year. Monitoring zoonotic viruses is essential, as viruses evolve naturally through mutation, rearrangement, or recombination, becoming more virulent or transmissible. Emerging swine viruses threaten herd health and have caused losses in the last decades. Factors contributing to these phenomena include failures in biosecurity, biocontainment, and herd immunity imbalance. The world is alerted to highly pathogenic avian influenza outbreaks in wild or domestic birds and mammals. As it is a zoonosis and a virus in constant evolution, it is essential to be prepared for an effective response and surveillance. However, we must think less about species and more about systems. The impact of pandemics like COVID-19 on human health and the global economy is immense, emphasizing the importance of integrating human, animal, and environmental health approaches. One health implementation is crucial to avoid the drivers of disease emergence or spillover factors. It also deals with developing and adopting effective public disease surveillance, prevention, response, and control policies. Everything is connected and complex, with multisectoral and multidisciplinary work being essential. However, implementing One Health is much more than zoonoses; it includes nutritious foods, food safety, antimicrobial resistance, and many other aspects of environmental health.

1. INTRODUCTION

In the past decade, the emergence of diseases, including pandemics, has highlighted the importance of these problems to the health of all living elements (Zanella, 2016; Zanella and Zanella, 2023). Global health includes human health and the integration of health approaches, with the core of this umbrella containing the definition of One Health (Gruetzmacher et al., 2020). This includes the integration of human, animal, and environmental health, considering the inseparability between them (Adisasmito et al., 2022). Environmental health deals with ecological and social interactions, and planetary health is about human civilization and the state of natural systems (Gruetzmacher et al., 2020).

Agriculture and livestock are essential sectors for many nations' economies, and zoonotic diseases caused by agents transmitted from non-human animals to humans affect more than two billion people worldwide, causing more than two million deaths every year (Bank, 2021). Zoonoses account for up to 75% of newly discovered or emerging infectious

diseases (EIDs) and 60% of recognized contagious illnesses in the last century, causing significant local, regional, and global disease burdens (Brown, 2004; Jones et al., 2008; Taylor et al., 2001).

Due to their high occurrence and severity, swine viral diseases (SVDs) are one of the most studied emerging animal diseases. SVDs are a significant concern due to their high occurrence and severity, impacting pig health and human health. Also, pork products are essential in many countries' economies and protein supply. Despite advancements in pork production systems, animal diseases still account for 20% of losses. In addition to recently discovered viral agents that have affected swine herds, more viruses might be circulating, posing a zoonotic risk and moderate to serious human health risks (Lin et al., 2023). EIDs in swine include endemic, foodborne, transboundary diseases, idiopathic vesicular, and subclinical infections. Traditional pig husbandry techniques have undergone significant modifications due to the growth and intensification of pig production, creating an environment favorable to the establishment and spread of infectious illnesses. Because of this, pigs are becoming intermediate and more abundant hosts for viruses that have the potential to cause a pandemic (Lin et al., 2023). Thus, factors contributing to these matters include biosecurity failures, biocontainment, and herd immunity imbalances. In addition, viruses evolve naturally through mutation, rearrangement, or recombination, making monitoring their evolution crucial.

This work will discuss the importance of emerging viral diseases, emphasizing zoonotic viral diseases with epidemic or pandemic potential. In addition, it will discuss SVDs that appeared in the last decades and how they are impacting the current production system.

2. VIRUSES AS THE MOST FREQUENT EMERGENT ZONOTIC PATHOGEN

EIDs are a critical global health concern, with zoonoses dominating (60.3%), primarily from wildlife. A study analyzing 335 EID events between 1940 and 2004 found non-random global patterns, with zoonoses dominating (60.3%) (Jones et al., 2008). Of 1415 pathogenic infectious organisms, 61% are zoonotic and can be transmitted between humans and animals. Out of these, 75% are twice as likely to be associated with emerging diseases than non-zoonotic pathogens (Taylor et al., 2001). RNA viruses are the most common emerging zoonotic agents, particularly RNA viruses, which infect various hosts, including domestic or wild animals (Woolhouse and Gowtage-Sequeria, 2005).

The International Committee on Taxonomy of Viruses (ICTV) has a database of 4958 virus species and 1479 vertebrate virus species, with viral traits and host ranges predicting confirmed zoonotic, potential zoonotic, and disease emergence outcomes (Singh et al., 2022). Bat- and livestock-adapted viruses pose a high risk, with 39 predicted with never-reported zoonotic potential or potential human virus emergence.

The World Health Organization's (WHO) priority pathogen list includes COVID-19, Crimean-Cong hemorrhagic fever, Ebola virus disease, Marburg virus disease, Lassa fever, MERS, SARS, Nipah, henipaviral diseases, Rift Valley fever, Zika, and Disease X (WHO, 2022). Machupo, known as "black typhus" and Bolivian hemorrhagic fever, are significant public health risks (Meadows et al., 2023; Zhong and Huang, 2019). The number of viral spillover events from animals to humans increased by 5% annually from 1963 to 2019, causing around 1,216 deaths in 2020. If the rate continues, four times the number of outbreaks will occur by 2050, causing 12 times the number of deaths, around 15,000 a year. Most of the 72 outbreaks were caused by filoviruses in Africa, such as Marburg and Ebola, which caused more than 90% of the 17,000-plus total deaths. There are no licensed vaccines for all Ebola strains, but some are developing for Marburg (Meadows et al., 2023; Zhong and Huang, 2019).

The Henipavirus genus includes two highly virulent zoonotic viruses, Hendra and Nipah, which are primarily bat-borne and have outbreaks in Australia and Southeast Asia. Its natural reservoir is fruit bats. Hendra, another henipavirus, was first observed in Australia in 1994 (Meadows et al., 2023). Both cause respiratory illness and flu-like symptoms, potentially leading to encephalitis (Bruno et al., 2023; Meadows et al., 2023). Nipah kills between 45% and 75% of infected individuals. No licensed vaccines exist (Meadows et al., 2023). Besides those continents, there is limited evidence in the Americas for the circulation of these viruses (Hernández et al., 2022). A novel henipa-like virus was discovered in Brazil from opossums, and the virus was named Peixe-Boi virus (PBV). The study used next-generation sequencing and metagenomic approaches to find the original evidence of a henipa-like virus genome in Brazil and South America, as well as the first description of a henipa-like virus in marsupial species (Hernández et al., 2022).

Coronaviruses, such as SARS-CoV-2, have become a significant public health concern in the 21st century. The WHO declared the outbreak a public health emergency of international concern and a pandemic. Extensive surveillance of SARS-CoV-2-related viruses in China, Southeast Asia, and other regions will help to understand its zoonotic origin. Climate change-driven increase in bat richness in the southern Chinese Yunnan province and neighboring areas in Myanmar and Laos may have played a vital role in the evolution of transmission of these coronaviruses (Beyer et al., 2021).

Influenza viruses are classified into four types: A, B, C, and D, with A and B causing seasonal flu epidemics (Webster and Krauss, 2002). Influenza A viruses (IAV) are zoonotic and cause global pandemics when a new, different virus emerges. IAV caused four pandemics in the last century (Saunders-Hastings and Krewski, 2016). Introducing swine or avian influenza viruses into the human population can set the stage for a pandemic, with concerns about the Highly Pathogenic Avian Influenza Virus (HPAIV) becoming the next pandemic. Regarding IAV in pigs and zoonotic spillover, control measures include avoiding human virus introduction into pigs and vaccinating pig farming workers.

3. DRIVERS OR FACTORS FOR ZONOSE EMERGENCY AND SPILLOVER

The human population's expansion, with an estimated 10 billion people by 2050, is likely to contribute to the emergence of new diseases. This growth and urbanization will stress the need for sustainable energy and food production, increasing the likelihood of future pandemics. Population diversity, including cultural, genetic, educational, structural, environmental, and socioeconomic diversity, may cause some populations to be more vulnerable to diseases or prone to

distribute diseases (Simpson et al., 2021; Mettenleiter et al., 2023; OHHLEP et al., 2023). Climate change, war, conflict, and environmental degradation are causing increased human and animal displacement, disrupting socio-economic structures, weakening the immune system, and increasing susceptibility to infectious diseases. Climate change also causes a rise in zoonotic diseases, affecting the survival, reproduction, and distribution of hosts, pathogens, and vectors in urban areas and the interaction between humans and animals. As a consequence, it has caused a global spread of rodents, rodent-borne pathogens, and bats. Deforestation, altered microclimates, and habitats have led to the spread of common disease vectors like mosquitoes and ticks causing changes in pathogen prevalence. Land conversion also increases accessibility to blood meals, with wild, domesticated animals near humans. It is unknown how many pathogens are transmitted to wildlife by mosquitoes, and many other parasites and undiscovered viruses are still poorly studied. Anthropogenic factors also affect animal health, and livestock is often the only moveable asset during disasters, but its inclusion in humanitarian responses can lead to fragmentation. Wild boars spread throughout Europe, Asia, Africa, and the Americas, have led to the spread of infectious diseases such as African swine fever (ASF), classical swine fever (CSF), and Aujeszky's disease (AD) and hepatitis E (HE).

In summary, zoonotic diseases have increased due to population growth, urbanization, climate change, mobility, global trade, intensive livestock farming, agricultural expansion, land use changes, habitat fragmentation, and biodiversity loss. Factors such as pollution, environmental degradation, social imbalance, population deprived of liberty, and poor vaccine coverage are also important. Researchers warn that over the next 50 years, at least 15,000 viruses will spread between species due to the climate crisis (Carlson et al., 2022). Bats, an important mammal vector, will account for most disease spread due to their ability to travel large distances. Studies predict that deaths from zoonotic viruses will increase 12-fold by 2050 due to climate change and habitat encroachment (Meadows et al., 2023; Prater, 2023).

4. CHALLENGES ON SWINE DISEASES

The swine industry faces economic risks due to modernization, high technology, costly genetics, and complex production systems. Pathogens, including endemic, emerging, and re-emerging agents, continue to cause concern and losses in performance and mortality for this industry. The emergence of pathogens, especially zoonotic ones, is increasing globally, and despite high costs and technology, there are difficulties in intensively producing pigs. Challenges also include monitoring, controlling, and eradicating emerging diseases due to the interrelation of production and the globalization of the industry. The imprudent use of antimicrobials increases pathogen resistance, and the fight against bacteria becomes harder. For viruses, vaccine failures due to variants evolution create possibilities of continuous transmission, mutation accumulation, and risk of spillover between species.

Based on what has emerged, EID in pigs can be classified as follows: 1) transboundary swine pathogens introduced into new regions; 2) endemic swine pathogens that changed pathogenicity or mode of transmission; 3) non-swine animal pathogens that entered swine populations; and 4) non-pathogenic zoonotic agents that entered swine populations (Davies, 2012).

As mentioned, viruses are the most common EID agent and SVDs that deserve attention are influenza A virus (IAV), porcine circovirus type 2 (PCV2), Seneca Valley Virus or Senecavirus A, Porcine Epidemic Diarrhea Virus (PEDV), Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), African Swine Fever Virus (ASFV).

Other agents such as novel porcine parvovirus (nPPV), porcine enterovirus, porcine sapelovirus (PSV), porcine Kobuvirus (PKBV), porcine torque teno sus viruses (TTSuV), porcine bocavirus (PBoV), porcine toroviruses (PToV), porcine lymphotropic herpesviruses (PLHV), porcine hepatitis E virus (swine HEV or Paslahepevirus balayani or HEV), and porcine sapovirus (porcine SaV), which although the clinical importance is not yet evident, are present in lesions or accompanied in clinical cases with other agents.

In addition, new emerging viruses such as atypical porcine pestivirus (APPV), PCV3, PCV4, SADS-CoV, influenza D, and others with regional or global distribution and with unclear pathogenesis pose a new challenge to veterinary medicine (Perfumo et al., 2020).

Viral evolution is a never-ending process in which the virus adapts to the host's or environment's pressure. It can occur in various ways, but the end goal is to create a progeny virus with advantages that differ from the original. Viruses, mainly single-stranded RNA and DNA viruses that have a high mutation rate (10⁻⁴/10⁻⁵ nucleotides per replication cycle), can change in virulence either by rearrangement, recombination, or mutation, which eases their adaptation to the innate immune response (Shi et al., 2018). Relevant examples are HP PRRSV (highly pathogenic PRRSV) (An et al., 2020)(18), influenza A H1N1pdm09 (pandemic influenza virus) (Al Farroukh et al., 2022), and PEDV (Jung et al., 2020).

Some viruses have presented as subclinical for a long time and were only discovered due to the development of metagenomics or next-generation sequencing techniques. Viruses such as PCV3, SADS-CoV (swine acute diarrhea syndrome coronavirus), and LINDA (novel pestivirus causing congenital tremor known as lateral-shaking inducing neurodegenerative agent) have been identified using the techniques described above (Perfumo et al., 2020)). Modern techniques also have studied retrospective materials and showed previously unidentified viral agents. One example is astrovirus 4 (PoAstV4) in pigs with respiratory disease but of unknown etiology. Even though five known lineages of astroviruses were previously identified in pigs as causing gastroenteritis, neurologic disease, or asymptomatic infection, PoAstV4 is considered a new respiratory disease agent (Rahe et al., 2023).

Another example is the porcine parvoviruses (PPVs) (Vargas-Bermudez et al., 2023), present on all continents, with the highest prevalence in finishing pigs. Eight PPVs are known in the swine host, with PPV1 being the oldest and the primary agent of SMEDI. The pathogenesis of the novel PPVs (nPPVs), PPV2 through PPV8 is still undetermined. PPVs are structurally similar, with differences mainly at the genomic level. Mutations in the VP protein affect virulence, tropism, and viral antigenicity. nPPVs have mutation rates similar to ssRNA viruses, with the highest mutation rate reported for

PPV7. The relationship between nPPVs and clinical manifestations is complex, but some evidence suggests associations with the porcine respiratory disease complex (PRDC). Further research is needed to establish nPPVs as disease agents, their effect on coinfections, and their impact on swine health (Vargas-Bermudez et al., 2023).

Even more complex, a study found a circular replication-associated protein (Rep)-encoding single-stranded (CRESS) DNA virus [named Po-Circo-like (PCL) virus] in intestinal tissue and fecal samples of pigs. The virus may be responsible for viral genome replication and cause diarrhea symptoms in pigs. Four strains were identified in two pig farms in Hunan Province, China, sharing 85.7-99.5 percent nucleic acid and amino acid identity with the reference strains. Further investigation is needed to determine the virus's pathogenesis and epidemiologic impact (Ji et al., 2023).

As mentioned previously, pigs are thought to be significant reservoirs for the emergence of new reassortant IAV strains that have the potential to spread globally. Numerous viruses that can infect humans can be found in backyard farms, commercial swine herds, and wild pigs. These viruses can range from those known to be emerging and endemic in humans to those with a high potential for becoming pandemics, having significant implications for public health. Other examples include the previous outbreaks of Japanese encephalitis (JEV) and the Nipah virus (Glud et al., 2021; McLean and Graham, 2022). Encephalomyocarditis virus (EMCV) causing disease emergency also has been documented in commercial growing-finishing pigs from two farms in Midwest Brazil. This virus was previously detected in humans and rodents in South America; and in Brazil, it was reported in wild animals and horses. The study found cardiomegaly, myocardial necrosis, and fibrosis in pigs and rats (Gris et al., 2023).

Regarding HEV, several studies show that HEV is ubiquitous in swine populations with no clinical signs. Yet, human contact with swine-infected HEV zoonotic genotype 3 can develop the disease. The virus can be found in pig farming effluents and a few pork products (Heldt et al., 2016; Pereira et al., 2018). Therefore, actions to control the infection in swine herds and exercise caution while handling food, especially pig liver, are pertinent (Soares et al., 2022).

Finally, pigs can be susceptible to experimental infections of other species' viruses, like the clade 2.3.4.4b HPAIV (Kwon et al., 2023), Reston virus (RESTV, an Orthoebolavirus genus) (Lewis et al., 2024) or Zika viruses (Pena et al., 2018; Sabir et al., 2023), and consequently have the potential to spread to humans.

5. DRIVERS OF PATHOGEN EMERGENCY IN SWINE

As with human EID, the drivers for EID in swine populations are not clear. However, as the increase of human population being one important driver for EIDs in public health, in swine, increased density and intensity of swine production are also significant. In the current scenario, high animal densities, quick animal turnover rates in confinement buildings, and more genetic homogeneity among swine herds are the outcomes of this enhanced intensification, which may make the animals more susceptible to illness.

Other essential factors include altered management practices, the interaction with wild animals, environmental changes, and pathogen acquisition of new virulence factors (Bekedam, 2006; Zanella, 2016). In summary, most reasons are imposed by human intervention, which directly or indirectly disrupts the host-pathogen equilibrium or causes EID introduction into a new territory due to human mobility or trade (Cutler et al., 2010). In swine farming, it is no different; most of the diseases emerging in recent decades already occurred in herds or regions in a balanced manner but were distributed, or their pathogens acquired essential virulence factors for manifestations of pathological syndromes, previously unknown (Drew, 2011).

This is how many infectious agents have emerged and will continue to emerge. Although viral selection and evolution are typically viewed as a precursor to an advantage (easier transmission, host diversity, environmental resistance, or immune response evasion), some mutations can and will result in adverse changes in the virus and may cause disadvantages for the pathogen. Consequently, this is logical when the entire process is analyzed as equilibrium. An example is the transmissible gastroenteritis virus (TGEV), which caused significant losses to the pig industry. In 1987, another coronavirus, known as porcine respiratory coronavirus (PRCV), a variant more transmissible than its predecessors, emerged. PRCV causes a mild respiratory infection and provides herd immunity for TGEV (COHEN, 2022). Later, another enteric coronavirus, PEDV, re-emerged in China in 2010 but from a highly virulent isolate, reaching the United States and other countries causing enormous losses, showing that the coronavirus "saga" is not over. Therefore, detecting new viruses and their variants is crucial for disease control, as random mutations, rearrangements, or viral recombination can occur (Cui et al., 2019).

In brief, the drivers of pathogen emergence in swine populations can be due to many circumstances. But can be summarized into two factors. The first is probabilistic, i.e., the threat has always been present, and emergence is simply a matter of time. The second factor, which is generally discussed more (and is very difficult to prove), is the changing ecology of these pathogens, environment, and host, among others (Drew, 2011).

6. EVOLUTION AND CHANGES IN THE PIG PRODUCTION

Pig industry has evolved in recent decades to increase productivity, leading to pathogen horizontal transmission. Genetic changes, weight gain, feed conversion, and lean meat have caused imbalances in pigs' cardiorespiratory and immune capacities. Intestinal ecology has also changed due to feed ingredients and medications. Vaccines are a reliable tool against infectious agents, but their intense use may drive virus evolution and require high surveillance. Misuse of vaccines can lead to viruses leaking through immune responses (Drew, 2011; VanderWaal and Deen, 2018).

Interspecies transmission means the infection of the potentially pathogenic agent in a new host, such as IAV, between migratory waterfowl and humans. Other examples include bats as the source of the Nipah virus and porcine acute diarrhea syndrome (SADS coronavirus). Recent work has found porcine PCV3 to have high homology with PCV1 from bats. The rising proximity between species due to multiple factors can allow viruses to "jump" the species barriers. Interspecies transmission of viruses occurs frequently, but it does not always end in a pandemic because there are multiple steps that the

virus must pass through to be considered a risk to the novel host species. First, the original host must carry and shed the virus. Second, the novel host has to be exposed to the original to a great extent. Third and fourth, the virus has to be capable of infecting the new host and replicating well in it (these steps involve more complicated factors, like receptor availability and affinity, intensity of infection, and immune response) and finally, to complete the jump the novel host has to be able to shed the virus effectively to others of his species (Plowright et al., 2017).

Swine viruses threaten human health, and vice versa, because of the close contact and similarities between the two species. In many ways, humans and pigs are anatomically similar. Both species express the sialic acid α -2,6-terminal saccharides on their upper respiratory tracts, which are preferred receptors for IAV. The same virus can easily infect both species (Nelson and Vincent, 2015). This example emphasizes the need for a “big picture” surveillance approach on these agents. Humans have been and will continue to be responsible for stimulating the emergence and mutation of viruses in swine herds and their direct introduction.

7. CONCLUSIONS

Globalization has increased the threat of pandemics and accelerated global transmission but also facilitated international cooperation, disease research, and surveillance. To prevent zoonotic spillover is essential to identify threats. The strategy involves health surveillance, addressing disease emergence drivers like climate change, land use, wildlife trade, and food systems. Most transmission routes of zoonoses in humans are associated with direct exposure to infected pigs or raw or undercooked pork products. Thus, developing risk reduction activities like biosecurity and vaccination for infection prevention, including occupational diseases such as IAV, is essential. Measures to limit future zoonoses also include attention to live-animal markets, food consumption habits, exotic animal farms and reducing habitat destruction. Multidisciplinary approaches and public policies are needed, as well as joint efforts from veterinary, human medical, and public health professionals.

The swine industry is ahead of the curve in controlling pig diseases, but there are opportunities to capitalize on its strengths. The first step is to reduce the economic impact on production, increase herd immunity, and increase biosecurity to prevent transmission and spread of infection to other stages or herds. Biosecurity is not a novelty in pig farming, and new diseases have emerged in areas lacking it. Biosecurity is also threatened during financial crises, war, or migration. Biocontainment, which uses filtered air to prevent pathogen dispersal, is still restrict, but its success is estimated to be significant. Herd immunity is crucial, as swine health is a population issue. Population density, concentration of immunocompromised populations, co-infections, sanitation levels, aerosol concentration, and agonistic behavior must be considered to limit the likelihood of transmission.

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