

# One health approach for the surveillance of novel swine viral diseases

## Uma abordagem de saúde única para a vigilância de novas doenças virais de suínos

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### Abstract

The novel coronavirus pandemic highlighted the importance of discussing and monitoring emerging diseases to scientific society, particularly in the case of zoonotic diseases. Diseases emerge in nature and infect living beings current on all continents, even in the current scenario of biomedical research evolution. Among the most studied emerging animal diseases are the swine viral diseases, due to their high occurrence and severity. Added to this, is the economic impact on the health of pigs and in some cases on human health. The challenges of swine health include endemic diseases, foodborne and transboundary diseases. Idiopathic vesicular diseases and subclinical diseases have also been identified, either alone or in combination with other infections. Several factors have contributed to these phenomena, but failures in biosecurity, biocontainment, and herd immunity imbalances are critical and must be addressed. Viruses evolve naturally, through mutation, rearrangement, or recombination, either to become more virulent or more transmissible, or not. This review will discuss the broad field of emerging swine viral infections, how monitoring the evolution of these viral agents is of supreme importance. Also, when should a new disease or emerging agent is considered a risk to swine production? Although the evolution of pork production systems is admirable, animal diseases continue to account for 20% of the losses. Therefore, international organizations work with member countries to prevent animal diseases, ensure food supply, maintain household income, health, and preserve the future. One Health is not just a concept, but an action of surveillance and control that all countries must implement.

**Keywords:** Emergence; Evolution; Pig Disease; Public Health

### Resumo

A pandemia do novo coronavírus enfatizou a importância que a discussão e a vigilância de doenças emergentes representam para a sociedade científica, especialmente no caso de doenças zoonóticas. Mesmo no atual cenário de evolução da pesquisa biomédica, as doenças surgem na natureza e infectam os seres vivos em todos os continentes. Entre as doenças animais emergentes mais estudadas estão as doenças virais suínas, devido à sua alta ocorrência e gravidade. Soma-se a isso o impacto econômico na saúde dos suínos e, em alguns casos, na saúde humana. Os desafios da saúde suína incluem doenças endêmicas, doenças transmitidas por alimentos e doenças transfronteiriças. Além disso, doenças vesiculares idiopáticas e doenças subclínicas foram identificadas isoladamente ou em co-infecções. Vários fatores desencadearam esses fenômenos, mas falhas na biossegurança, biocontenção e desequilíbrio na imunidade do rebanho são fundamentais e devem ser corrigidos. Os vírus evoluem naturalmente, por mutação, rearranjo ou recombinação, para se tornarem mais virulentos ou mais transmissíveis, ou não. Esta revisão discutirá o amplo campo de infecções virais suínas emergentes e como o monitoramento da evolução desses agentes virais é de suma importância. Além disso, quando considerar uma nova doença ou agente emergente um risco para a suinocultura. A evolução dos sistemas de produção de suínos é admirável, mas as doenças dos animais ainda respondem por 20% das perdas. Portanto, as organizações internacionais trabalham com os países membros para prevenir doenças animais, garantir o abastecimento de alimentos, manter a renda familiar, a saúde e preservar o futuro. Saúde Única não é apenas um conceito, mas uma ação de vigilância e controle que todos os países devem implementar.

**Palavras-chave:** Doença de suínos; Emergência; Evolução; Saúde Pública

## 1. Relevance of animal health in swine production

One of the most difficult challenges in swine production<sup>(1)</sup>. The occurrence of porcine epidemic diarrhea in the United States<sup>(2)</sup> and African swine fever in Europe-Asia-Caribbean<sup>(3)</sup> in recent years has alerted the

swine industry to the need to develop more agile mechanisms for monitoring, detecting, controlling, and the eradicating emerging diseases in swine production. One of the most important factors is the interrelation of production. The world has never been so connected to this modern and complex production structure, which allows for the transfer and transport of animals and

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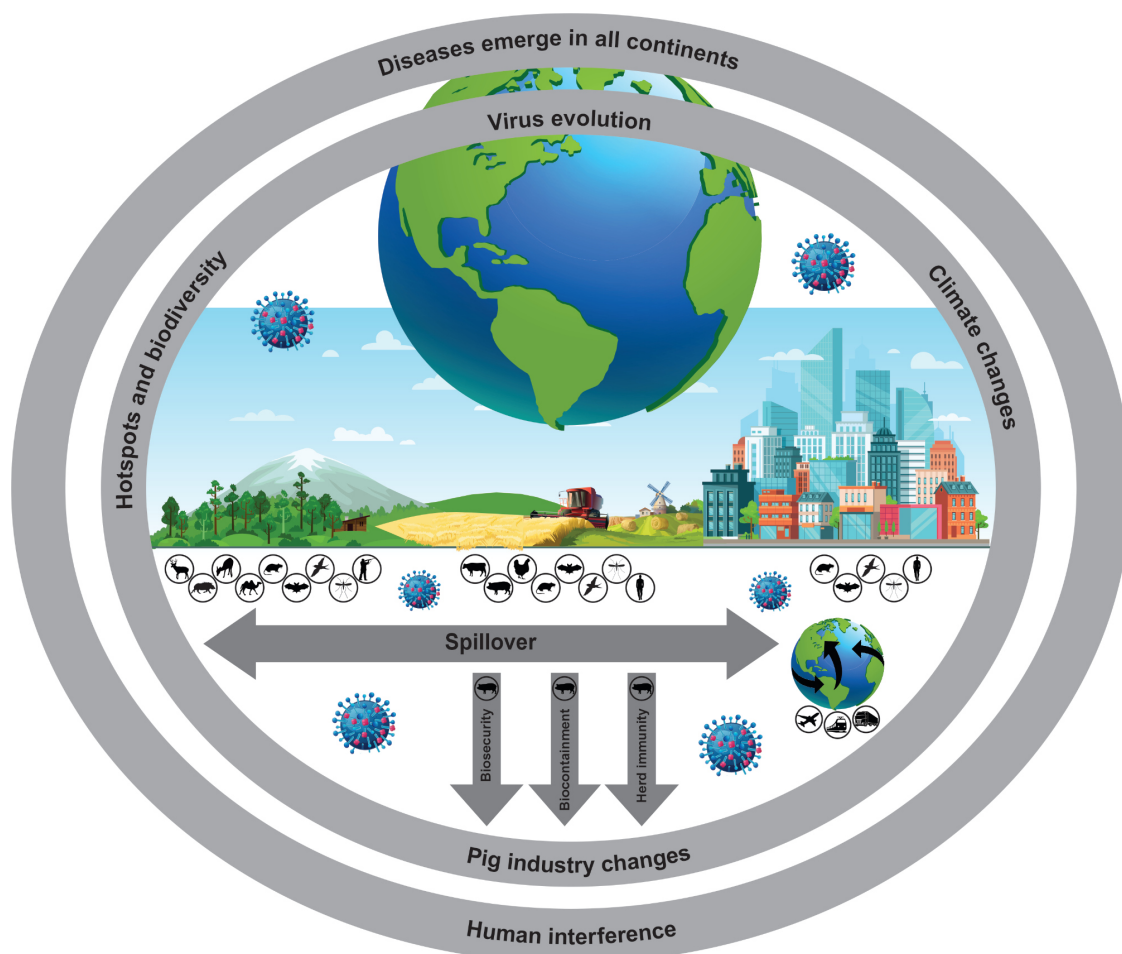
supplies between different locations on the planet<sup>(4)</sup>. Brazil is the fourth world producer and exporter and in Brazil alone 350 thousand pigs are transferred daily<sup>(1, 5)</sup>. Parallel to this, the modernization of operations, greater technology employed, larger farms, and consequently high capital invested and the interconnection in all links of the chain raise the economic risk of the activity<sup>(6)</sup>.

Pathogens that cause diseases, whether endemic, emerging, or re-emerging, will always be a source of concern and loss, both in terms of performance and mortality<sup>(7)</sup>. However, the increase in the emergence of pathogens, especially zoonotic ones, in the world has recently drawn the attention of researchers<sup>(8)</sup>. Furthermore, this is happening on all continents, even with all the technology and high costs invested in medications and vaccines, there are difficulties in producing pigs intensively without the interference of infectious agents, viral or bacterial<sup>(9)</sup>. The ubiquitous irresponsible use of antimicrobials, for example, only

increases the challenges with pathogen resistance and the fight against bacteria only becomes harder. For viruses the challenge is in vaccine failures that due to the emergence of variants, create possibilities of continuous transmission, consequently accumulation of mutations, and risk of spillover between species<sup>(10)</sup>. Figure 1 depicts a graphical summary of the topic covered in this review.

## 2. Emerging swine diseases

The cause of disease emergence are poorly known and understood, but the main one is the human population growth<sup>(11, 12)</sup>. Other important factors include urbanization, intensive animal production, altered management practices, interaction with wild animals, environmental changes, and pathogen acquisition of new virulence factors<sup>(11, 12)</sup>. In summary, most factors are imposed by human intervention, which directly or indirectly disrupts the host-pathogen equilibrium<sup>(9, 14)</sup>. In swine farming it was no different, most of the diseases



**Figure 1.** Graphic summary of the subject addressed in this review. The figure shows that emerging diseases appear in nature, infect living beings, and can spillover to the human population. Several factors have contributed to these phenomena, including climate change, biodiversity (hotspots), viral evolution, transport, and human interference. However, regarding pig industry, the failures in biosecurity, biocontainment, and herd immunity imbalance are critical and must be addressed.

emerging in recent decades already occurred in farms in a balanced form, and their pathogens ended up acquiring important virulence factors for manifestations of pathological syndromes, previously unknown<sup>(6)</sup>. This is how many pathogenic types of various infectious agents have emerged and will continue to emerge. Examples of these agents are listed below:

Viral agents: influenza A (H1N1pdm) virus, 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. Other agents such as 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), and porcine sapovirus (porcine SaV), which although the clinical importance is not yet clear, are present in lesions or accompanied in clinical pictures with other agents. In addition, new emerging viruses such as atypical porcine pestivirus (APPV), PCV-3, SADS-CoV, influenza D, and others with regional or global distribution pose a new challenge to veterinary medicine<sup>(15)</sup>.

Based on what has emerged, emerging diseases can be classified as follows: 1) endemic swine pathogens that change in pathogenicity or mode of transmission; 2) non-swine animal pathogens that enter swine populations; and 3) non-pathogenic zoonotic agents that enter swine populations<sup>(6, 16)</sup>.

Viral evolution is a never-ending process in which the virus adapts to the host's or environment's pressure. It can be done in a variety of ways, but the end goal is the same: to create a progeny virus with advantages that differ from the original. Changes in virulence either by rearrangement, recombination or mutation of swine viruses, mainly single-stranded RNA and DNA viruses that have a high mutation rate (10-4/10-5 nucleotides per replication cycle), which facilitate their adaptation to the innate immune response is evolution<sup>(17)</sup>. Relevant examples are HP PRRSV (highly pathogenic PRRSV)<sup>(18)</sup>, influenza A H1N1pdm09 (pandemic influenza virus)<sup>(19)</sup>, and PEDV<sup>(20)</sup>.

Some viruses have been present as subclinical infections for a long time and were only discovered due to the development of metagenomic 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 neuro-degenerative agent) have been identified using the techniques described above<sup>(15)</sup>.

The drivers of pathogen emergence in swine populations can be due to 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 as mentioned above<sup>(6)</sup>.

Although viral selection and evolution are typically viewed as a precursor to an advantage (easier transmission, environmental resistance, or immune response evasion), some mutations can and will result in negative changes in the virus and may cause disadvantages. Furthermore, when the entire process is analyzed as equilibrium, this is understandable. In 1946, veterinary researchers at Purdue University in the USA reported a severe gastrointestinal viral disease in piglets. The disease that could be reproduced after offering diseased pig intestines to healthy piglets proved to be a coronavirus, called transmissible gastroenteritis virus (TGEV). TGEV is not a zoonosis, but it caused many losses to the world pig industry in the 1970s. However, TGEV took a strange turn: the disease basically disappeared when a variant of TGEV that was even more transmissible, but less harmful, essentially immunized pigs against the original virus. "The best coronavirus vaccine was made by nature," says Stanley Perlman, veteran coronavirus researcher at the University of Iowa, USA. Litters tested positive, but without clinical signs of diarrhea. In 1984, Pensaert and coworkers in Belgium discovered that the TGE-related virus triggering antibody production and protecting litters actually had a different tropism. Instead of gastrointestinal cells, the mutant infected the trachea, bronchi, and lungs, earning it the name porcine respiratory coronavirus. According to The Ohio State University researcher Linda Saif, PRCV emerged in the United States in 1989, and the genomic sequence differs from European isolates (1984), indicating that they emerged independently in both locations<sup>(21)</sup>.

Like the Omicron variant of COVID-19, PRCV is transmitted more easily than its predecessors are. Moreover, sequencing of TGEV and PRCV revealed that in the surface protein S gene there was a deletion of more than 600 nucleotides, although this deletion does not affect the binding of the viral protein to the cellular receptor, but to sialic acid, a molecule present in intestinal mucus, so PRCV does not infect the intestine. PRCV causes a mild respiratory infection and has provided herd immunity for TGEV<sup>(21)</sup>. However, the story of enteric coronaviruses did not end there. Another coronavirus from the same branch of the coronavirus family tree, PEDV, re-emerged in China in 2010, but from a highly virulent isolate, eventually reaching the United States and other countries in South and North America<sup>(2)</sup>. Despite the availability of PEDV vaccines, recombinant PEDV/TGEV has recently begun circulate<sup>(20)</sup>.

In conclusion, more transmissible and less virulent variants may emerge and aid in disease control. However, it is difficult to predict the next evolutionary step as random mutations, rearrangements, or viral recombinations are all possible, which emphasizes the importance of detecting new viruses and their variants.

### 3. Evolution and changes in the pig production

Pig production has undergone numerous changes in recent decades in pursuit of higher productivity, but all these changes have consequences. The advancements in production scale and systems favor pathogen horizontal transmission. The modifications in the genetics of pigs due to the search for more piglets per sow, better weight gain, feed conversion, and more lean meat in the carcass cause a misbalance in their cardiorespiratory and immune capacities. The “normal” intestinal ecology has also changed, due to the ingredients and medications provided in the feed. Vaccines are definitely a strong and reliable weapon against infectious agents. Nonetheless, it is confirmed that the intense use of vaccines is a factor that drives virus evolution, which is natural but necessitates a high level of surveillance that most countries cannot afford, and this before even considering vaccines misuse, which can lead to viruses “leaking” through the immune responses<sup>(6, 7)</sup>.

### 4. Emergence of human and swine viruses

Viruses do not evolve to become more dangerous in general<sup>(22)</sup>. According to research on various human pandemics, death tolls have gradually decreased since the middle ages. The reason we perceive diseases to be more dangerous today is that viruses spread much more quickly<sup>(23)</sup>. Furthermore, the reason for this is simply our way of life, which allows them to spread. Although not cause by a virus, the Black Death arrived in Europe on merchant ships. The plague had no chance of becoming a pandemic before they began traveling all over the world to and from Europe. Spanish flu was at its peak during World War I, a war the world had never seen before. The combination of crowded trenches and ports, as well as massive troop transport, was ideal for virus spread<sup>(23)</sup>.

Recent outbreaks, such as SARS, MERS, and the current COVID-19<sup>(24)</sup>, have occurred because we live in a way that allows for its spread. Contagion is aided by urbanization, globalization, and transportation. We have not only made it easier for viruses to spread, but we have also created an ideal environment for their evolution, with an abundance of susceptible hosts that adds to the risk of infection and the emergence of variants<sup>(23)</sup>.

Science evolves and new research tools are developed. As the field of molecular biology advances, the discovery of new viruses raises the need for a valid set of criteria to verify whether there is a causal

relationship between the presence of certain viruses and a specific disease, or even whether their presence is associated with a worse disease prognosis. A recent example was the discovery by the research group led by Amit Kapoor of a virus that shares characteristics with Hepatitis C virus (HCV) and human Pegivirus (HPgV; formerly known as GB C virus or hepatitis G virus)<sup>1</sup>; both, members of the family Flaviviridae<sup>(25)</sup>. The new virus, called human Hepegivirus-1 (HHpgV-1) is a blood-borne virus that was found in serum samples from two blood transfusion recipients and two hemophilia patients who received blood products. Several viruses have already been identified in blood to be transfused, many of them pathogenic (HCV, HBV, HIV) and others with no potential to cause disease such as TTV. So far, the two most relevant findings with potential medical impact were the long-term persistent viremia of HHpgV-1 in two hemophiliac patients and the genetic similarity between HHpgV1, highly pathogenic HCV, and apparently non-pathogenic HPgV1. As a result, epidemiological research papers from around the world are critical for learning about the prevalence and characteristics of this new blood-borne virus. Once available, such information will be extremely useful for developing new assays for its detection as well as avoiding false negative results when screening blood donors for its presence. To ensure the safety of this valuable medical and public health resource, surveillance of the various potentially blood-borne agents is required<sup>(25, 26)</sup>.

Viruses such as SARS-CoV-2 continually evolve as changes in the genetic code (genetic mutations) occur during genome replication. A lineage is a genetically related group of virus variants derived from a common ancestor. A variant has one or more mutations that differentiate it from other variants of SARS-CoV-2 viruses. As expected, several variants of SARS-CoV-2 were documented globally during this recent pandemic. In some cases, a group of variants with similar genetic changes, such as a strain or group of strains, may be designated by public health organizations as a Variant of Concern (VOC) or Variant of Interest (VOI) due to their shared attributes and characteristics that may require public health action. Omicron is a Variant of Concern (VOC)<sup>(27)</sup>.

Scientists have also been alarmed by the emergence of new human coronaviruses. The NeoCov coronavirus, discovered by Chinese scientists, is one example. According to the WHO, researchers in Wuhan discovered a new type of coronavirus, NeoCov, among bats in South Africa. More research is needed, but NeoCov is known to be closely related to Middle East respiratory syndrome, a viral disease discovered in Saudi Arabia in 2012. Furthermore, the study found that NeoCov, like the COVID-19 virus<sup>(28)</sup>, can enter human cells.



Interspecies transmission means the infection of potentially pathogenic agent in a new host, such as influenza A between migratory waterfowl and humans. Other examples include bats as the source of Nipah virus and porcine acute diarrhea syndrome (SADS coronavirus). Recent work has found porcine PCV-3 to have high homology with PCV-1 from bats. The rising proximity between species due to multiple factors can produce opportunities for 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 has to pass through to actually be considered a danger to the novel host species. First of all, the original host has to carry and shed the virus. Second, the novel host has to be exposed to the original at 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, immune response) and finally to complete the jump the novel host has to be able to shed the virus effectively to others of his own species<sup>(29)</sup>.

Swine viruses are a threat to 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  $\alpha$ -2,6-terminal saccharides on their upper respiratory tracts, which are preferred receptors for swine influenza virus. That is, the same virus can easily infect both species<sup>(30)</sup>. This example emphasizes the need for a “big picture” surveillance approach on these agents. Humans have been and will continue to be responsible for not only stimulating the emergence and mutation of viruses in the swine chain, but also for their direct introduction.

## 5. Challenges and opportunities

There are numerous possibilities. The swine industry is unquestionably “ahead of the curve” in many aspects pig disease control<sup>(6)</sup>. There are obstacles, but there is also an opportunity to capitalize on the industry's strengths<sup>(16)</sup>. The first step is to reduce the economic impact on production, prevention to increase herd immunity, and to increase biosecurity to prevent transmission and spread of infection to other stages or herds<sup>(31)</sup>.

Biosecurity is not a new in pig farming, and new diseases have emerged in areas where biosecurity is lacking<sup>(31)</sup>. Other species, such as bats or rodents, but also feral pigs should be avoided. This can be through direct contact, but also through consumption of food containing animal protein, including hunting meat. Biological compounds such as vaccines, which can become infected with other pathogens and carry them, are another potential source of exposure. In times of financial crisis,

war, or migration, biosecurity is jeopardized. Risks include, for example, the use of swill and the practice of subsistence farming in areas with diverse species such as mammals (pigs) and birds (ducks).

The second critical aspect is biocontainment, which is the use of measures (filtered air) to prevent pathogen dispersal. This measure is still understudied, particularly the economic impact of implementing such controls. Most facilities have air inlet filters but no outlet filters. The same is true for waste or washing water (including slaughterhouses). Given that we study biocontainment failures, the success of these measures is estimated to be significant<sup>(31)</sup>.

Furthermore, herd immunity is an important consideration. Despite the fact that individual pigs are infected, swine health is viewed as a population issue. Initially, the infection may spread and persist in a smaller population, but it eventually spreads to a larger population. This is because immunity varies greatly within a population. However, the emerging agent's ability to transmit must also be taken into account. Population density, concentration of immunocompromised populations, co-infections, sanitation levels, aerosol concentration, and agonistic behavior (fighting) have all been limited to the likelihood of transmission<sup>(31)</sup>.

## 6. Final considerations

Emerging diseases appear in nature, infect living beings on all continents, and have existed for a long time. Even with significant advances in research, diseases continue to emerge; emerging pig viruses have possessed a threat to herd health and caused losses, particularly in the last three decades. Several factors have contributed to these phenomena, but failures in biosecurity, biocontainment, and herd immunity imbalance must be addressed. It is critical to track the zoonotic ones, but not only these. Viruses evolve naturally, through mutation, rearrangement, or recombination, becoming more or less virulent, transmissible or not, and even disappearing. One Health is more than a concept; it is also a surveillance and control action that all countries must implement.

### Conflict of interest

The authors declare that no commercial or financial relationships that could be construed as a potential conflict of interest existed during the research.

### Author contributions

JRCZ's specific contribution included the conceptualization, funding acquisition, investigation, methodology, supervision, writing – original draft, writing – review & editing. GCZ's specific contribution to this work included the data curation, validation, writing – original draft, writing – review & editing.

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