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Exploring the clinical significance of Swine Influenza on pig farms in Germany

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Összefoglaló

Az *Orthomyxoviridae* család burkos vírusok csoportja, amelyek negatív irányultságú, egyszálú ribonukleinsavval (RNS) genommal rendelkeznek. A család kilenc nemzetséget foglal magában, amelyek közül az *Alphainfluenzavirus* kiemelkedő jelentőséggel bír, jellemzően gerincesek megbetegedéséért felelős. E nemzetség egyetlen faját, az influenza A vírust (IAV) jelentős klinikai és járványtani kórokozóként tartják számon.

A sertés influenzavírus (swIAV) az IAV antigén variánsa, világszerte jelentős gazdasági kárt okozó, a sertéspopulációkban széles körben elterjedt kórokozó. Az influenzavírusok négy típusa közül az IAV kiemelkedő jelentőségű mind az állat-, mind a humán közegészségügy szempontjából, mivel a múltban már számos nagy járványt okozott mind az emberek, mind a haszonállatok körében.

A swIAV egy rendkívül fertőző légzőszervi betegség, amely az év során ismétlődő hullámokban terjed, jelentős veszélyt jelentve az állategészségügyre és a sertéstenyésztés gazdasági eredményességére. A vírus pandémiás törzseinek evolúciója megnehezíti a járványok kordában tartását.

A swIAV egy releváns kórokozó, mivel képes olyan endémiás fertőzéseket kialakítani, amelyek gyakran enyhe, nem specifikus klinikai jelekkel járnak, így megnehezítik az időben történő felismerést. Ez lehetővé teszi a kórokozó számára, hogy hosszabb ideig észrevétlen maradjon a populációkban, akadályozva a járványok hatékony kezelését és a terjedés megfékezését.

Az újabb swIAV-törzsek, a klasszikus törzsekkel ellentétben, nemcsak egy-egy korcsoportot érintenek, hanem szélesebb spektrumú fertőzéseket okoznak. Ez a komplex fertőzési dinamika gyengíti az állomány immunitását, csökkenti a reprodukciós teljesítményt, elősegíti másodlagos fertőzések kialakulását, valamint jelentős mértékben csökkenti a gazdaságok termelési hatékonyságát. A betegség gazdasági következményei jelentősek, ideértve a megnövekedett kezelési költségeket, a hizlalási ciklus meghosszabbodását, a csökkent növekedési ütemet és a takarmányfelhasználás hatékonyságának romlását, amelyek mind jelentős pénzügyi veszteségeket eredményeznek.

A német sertéstenyésztési gyakorlatban bekövetkezett strukturális változások – kevesebb, de védekezés nehézségeit. A nagyobb, különböző korosztályokat egyesítő állományok kedvező feltételeket teremtenek a vírus folyamatos körforgásához, megnehezítve az állomány szintű fertőzések kontrollját, és növelve a tartós vírusos jelenlét kockázatát.

E kihívások fényében a swIAV elleni védekezés átfogó stratégiát igényel. A proaktív vakcinázás, valamint a fertőzési láncok megszakítását célzó intézkedések

kulcsfontosságúak. E stratégiákat szigorú biológiai biztonsági intézkedésekkel és hatékony korai felismerési rendszerekkel kell kiegészíteni, hogy minimalizálni lehessen a járványok okozta gazdasági veszteségeket, miközben az állatjóllétet is biztosítjuk.

Az állatorvosok és gazdák szoros együttműködése elengedhetetlen a swIAV diagnosztikájában és kezelésében. A hosszú távú védekezési stratégiáknak tartalmazniuk kell egyedi igényekre szabott oltási programokat, a gazdaságirányítás optimalizálását, valamint a szigorú biológiai biztonsági intézkedések bevezetését. Csak egy integrált, alkalmazkodó megközelítés révén lehet hatékonyan szembenézni a swIAV által támasztott folyamatos kihívásokkal, ezzel elősegítve a sertéstartó ágazat fenntarthatóságát és versenyképességét.

nagyobb, heterogénebb összetételű állományok kialakulása – tovább növelik a swIAV elleni.

Abstract

The *Orthomyxoviridae* family is a group of enveloped viruses with a negative-sense, single-stranded ribonucleic acid (RNA) genome. The family includes nine genera, among which the *Alphainfluenzavirus* is notable for causing diseases in vertebrates. Influenza A virus (IAV), the sole species of this genus, is a pathogen of great clinical and epidemiological importance.

Swine influenza A virus (swIAV) is an antigenic variant of IAV, a significant pathogen impacting pigs globally. As one of the four influenza virus types, IAV is highly significant both clinically and epidemiologically, having caused significant epidemics in livestock and humans in the past.

SwIAV is a highly contagious respiratory disease that circulates in recurrent waves year-round, posing substantial risks to animal health and farm productivity. Over time, the evolution of pandemic strains has further complicated its dynamics.

The virus is particularly problematic due to its ability to cause endemic infections with subtle and often ambiguous symptoms, which complicates early detection. As a result, the pathogen often remains undetected for extended periods, hindering efforts to control its spread and manage outbreaks effectively.

Unlike classical strains, which typically caused isolated outbreaks, these newer strains spread across multiple age groups. This complex infection pattern weakens herd immunity, disrupts reproduction, fosters secondary infections, and reduces farm productivity. The economic implications are significant, with increased treatment costs, extended fattening periods, reduced growth rates, and inefficient feed use all contributing to financial losses.

The structural changes in German pig farming, where there has been a shift toward fewer but larger, more heterogeneous farms, have exacerbated the challenges of managing swIAV. Larger herds with mixed-age groups create a conducive environment for continuous viral transmission, complicating infection control and increasing the risk of persistent viral circulation. Given these challenges, managing swIAV requires a multifaceted approach. Proactive vaccination to lower viral pressure, along with measures to break infection chains, is crucial. Coupled with strict biosecurity and early detection protocols, these strategies can help minimize the economic losses associated with influenza outbreaks while safeguarding animal welfare.

Collaboration between veterinarians and farmers is crucial for diagnosing and managing swIAV. Long-term strategies should include tailored vaccinations, improved farm management, and enhanced biosecurity measures to curb the spread of the virus and safeguard productivity. Only through a cooperative, adaptive management approach can the swine industry effectively address the evolving challenges posed by swIAV.

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Abbreviations

ELISA	Enzyme-linked immunosorbent assay
HA	Hemagglutinin
HI	Haemagglutination inhibition
IAV	Influenza A virus
M	Matrix
MMA	Mastitis, metritis, agalactia
NA	Neuraminidase
NAI	Neuraminidase inhibition
NP	Nucleoprotein
PA	Polymerase acidic
PB1	Polymerase basic 1
PB2	Polymerase basic 2
PCR	Polymerase chain reaction
PRCV	Porcine respiratory coronavirus
PRDC	Porcine respiratory disease complex
PRRS	Porcine reproductive and respiratory syndrome
PRRSV	Porcine reproductive and respiratory syndrome virus
qRT-PCR	Real-time quantitative reverse transcription polymerase chain reaction
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RT-PCR	Reverse transcription polymerase chain reaction
SA	Sialic acid
swIAV	Swine influenza A virus
VAERD	Vaccine-associated enhanced respiratory disease
WIV	Whole inactivated vaccines

I. Introduction

Swine influenza, a highly contagious respiratory disease caused by influenza A viruses (IAV), has evolved into a persistent and critical issue in the global swine industry, especially in regions with large-scale pig farming, such as Europe, North America, and Asia [1, 2].

The virus circulates year-round in these areas, presenting significant threats to animal health and farm profitability. Its widespread nature emphasizes the importance of addressing swine influenza, not only from a veterinary perspective but also in terms of economic stability and public health [3, 4].

In pigs, swine influenza typically presents as a respiratory illness with symptoms such as coughing, fever, nasal discharge, laboured breathing and decreased fertility. The severity of these symptoms may differ based on factors like the specific virus subtype, the health status of the animal, and the presence of co-infections. While mortality rates are generally low, the disease's high morbidity can lead to significant economic losses due to reduced growth rates, increased veterinary costs, and lower herd productivity [5].

Compounding these challenges, the management of swine influenza becomes even more difficult due to its immunosuppressive nature, which increases the occurrence of co-infections. Pigs often suffer from secondary bacterial infections which exacerbate respiratory symptoms and make treatment more complex. These co-infections increase the disease's severity and prolong recovery times [5].

Over time, the disease has shifted from an acute illness to a chronic, endemic infection, complicating management efforts, particularly on larger farms where the virus can remain undetected for extended periods. An infection chain often develops between sows and piglets of varying ages, allowing the virus to circulate persistently. The virus’s adaptability allows continuous evolution, complicating vaccine development and control measures [6].

The economic impact is significant, with farmers not only facing the costs of treatment and reduced productivity but also the ongoing expenses of implementing strict biosecurity measures. Effective control strategies are critical in managing swine influenza. While vaccination programs, biosecurity measures, and regular diagnostic testing play a key role, they must be continuously adapted to keep pace with the virus’s evolving nature. Such measures are essential not only for protecting animal health and farm profitability as well as for safeguarding public health [7].

This thesis will explore the clinical significance of swine influenza in German pig farms, focusing on the need for improved control strategies and addressing the practical challenges involved in managing this persistent disease.

II. Literature review

1. Aetiology

1.1. Taxonomy and morphology

The *Orthomyxoviridae family* (greek orthos: correct, right; myxa: mucus) includes enveloped viruses with a negative-sense, single-stranded and segmented ribonucleic acid (RNA) genome [8, 9]. It comprises of nine genera: *Alphainfluenzavirus*, *Betainfluenzavirus*, *Deltainfluenzavirus*, *Gammainfluenzavirus*, *Isavirus*, *Mykissvirus*, *Quaranjavirus*, *Sardinovirus* and *Thogotovirus* [10]. Viruses within the initial four genera are distinguished by variations in antigenicity in their nucleoprotein (NP) and matrix (M) proteins, are responsible for influenza diseases in vertebrates, encompassing birds, humans, and other mammals [11]. The IAV (species: *Alphainfluenzavirus influenzae)* is the only species of the *Alphainfluenzavirus* genus, and the swine influenza A virus (swIAV) is a variant of it [10]. Out of the four influenza viruses, they are the most significant pathogens clinically, having caused severe epidemics in both humans and domestic animals in previous instances [12].

Influenza virus particles demonstrate pleomorphism, with their envelope displaying both spherical and filamentous forms. Derived from host cell membranes, the virion envelope typically consists of irregularly shaped spherical particles measuring, which are 80–120 nm in diameter, or filamentous virions, measuring 20 nm in diameter and 200–300 nm in length. The genome of IAV comprises eight negative-sense RNA segments, each encoding one or two proteins (*Figure 1*). There are two types of surface spikes present on the viral envelope, the hemagglutinin (HA) and neuraminidase (NA) surface proteins. The first one is a rod-shaped, crucial for virus attachment to host cell sialic acid (SA) and envelope fusion, the second one is a mushroom-shaped and possesses NA activity. NA cleaves sialic acid from the cell surface, releasing the virus from the host cells [11]. These viral glycoproteins are attached to the viral envelope by short sequences of hydrophobic amino acids. The HA:NA ratio on virions is about four to one. Two M proteins are encoded on segment 7 of the IAV genome. M1 is the most copious protein in virus particles forming a protein layer under the viral lipid envelope, and M2 is an integral membrane protein transcribed from a spliced mRNA, which functions as an ion channel. This M protein shell surrounds the viral genome, accompanied by the NP and the following large proteins: polymerase basic 1 (PB1), polymerase basic 2 (PB2), and polymerase acidic (PA) [8]. It forms the ribonucleoprotein (RNP) complex responsible for RNA replication and transcription [13].

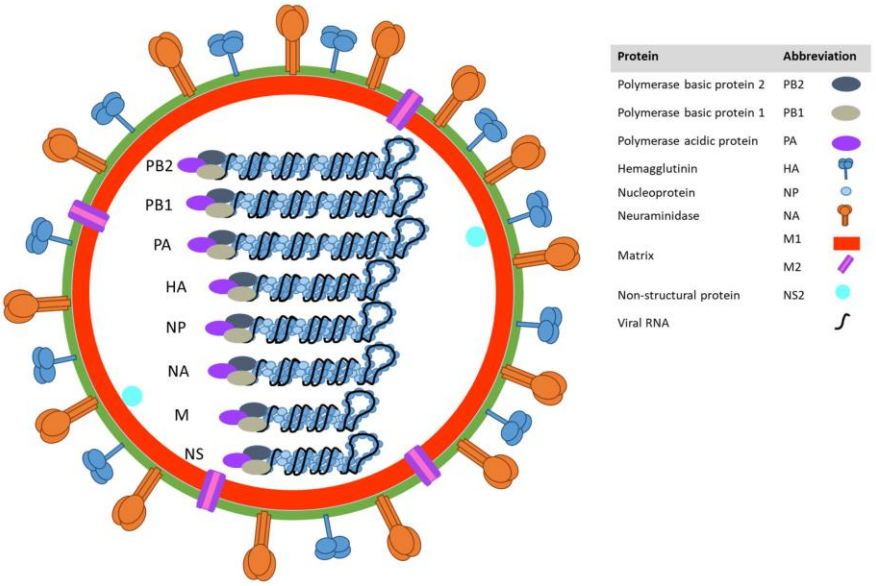

Figure 1: Structure of an Influenza A virion [14]

1.2. Genetic variability

IAV displays remarkable genetic flexibility. It may swiftly adapt to novel hosts and new virus variants can prevail within the population given the appropriate competence [15]. This can lead to an evasion of the host's adaptive immune response, alterations in pathogenicity or even shifts in host specificity [8, 16]. Regarding this aspect, the following mechanisms are considered.

1.2.1. Antigenic drift

IAVs are categorized into various subtypes according to the antigenic characteristics of their surface glycoproteins HA and NA projected from the surface of the envelope, of which there currently exist 18 HA and 11 NA subtypes [17]. The HA and NA genes of a virus are referred to as major targets for the immune response, with typically minimal or no cross-protection observed between different types of these proteins. Mutations induce gradual alterations in them, a process referred to as "antigenic drift" [9]. Due to the absence of proofreading capability of the influenza polymerase, a high gene mutation rate of roughly one error per replicated genome can be observed, meaning each cell has the potential to generate 10,000 new viral mutants, facilitating infection of neighbouring cells [18]. The Influenza A virus undergoes the most rapid mutations among the four types of influenza [19]. This aspect is of high importance to the evolutionary strategy of the virus [18].

1.2.2. Antigenic shift

Genetic reassortment occurs when the eight segments of the viral genome recombine in a single cell infected by two distinct viruses. If a host cell is infected by two different parent viruses at the same time, 254 genetically different reassortants can emerge [20]. This process can cause more rapid changes than the “antigenic drift” [12]. During virus genome replication in the cell nucleus, the resulting eight genome segments initially exist as individual RNPs. These are then combined in a process known as "assortment" to form virions with complete genomes [21].

However, IAvs often do not replicate all segments of the entire genome in precisely the same proportions and missing RNA segments can potentially be replaced by segments from a genetically distinct virus. It is possible for the viruses to reassort, whether they are adapted to the same host species or initially derive from different hosts. The fundamental requirements for genetic reassortment involve the encounter between viruses of two different genotypes requires them to infect the same host and the identical tissue within it, alongside genetic compatibility between parental strains [21, 22]. Reassortment may induce significant changes in viruses, potentially resulting in the emergence of viruses containing new HA, NA, or both. These sudden changes, referred to as "antigenic shifts," may enable the new virus to bypass the present immunity in its reservoir host.

The substantial variability among influenza viruses implies that two viruses with the same subtype may have only distant relationship to each other. Progeny viruses with combinations of eight segments derived from either parent may arise in case of co-infection of a single cell with two distinct parental strains of the virus [15]. While most of these reassortant viruses are inferior to the original viruses, this process is an important evolutionary mechanism. The exchange of genome segments leads to a tremendous variety of new virus strains with potentially entirely new characteristics [21, 22].

2. Dissemination

2.1. Host

IAV exhibits a broad host range, primarily residing in aquatic birds such as geese, ducks, waders, and gulls [23]. Wild water birds act as natural reservoirs, facilitating the spread of the virus to a wide variety of species. However, various other bird species can also become infected [24].

Key mammalian hosts include humans, pigs, and horses. Additionally, dogs, domestic cats, felid carnivores, several mustelid carnivores, marine mammals and additional species have been identified as accidental hosts, where stable transmission cycles are not established (*Figure 2*) [25].

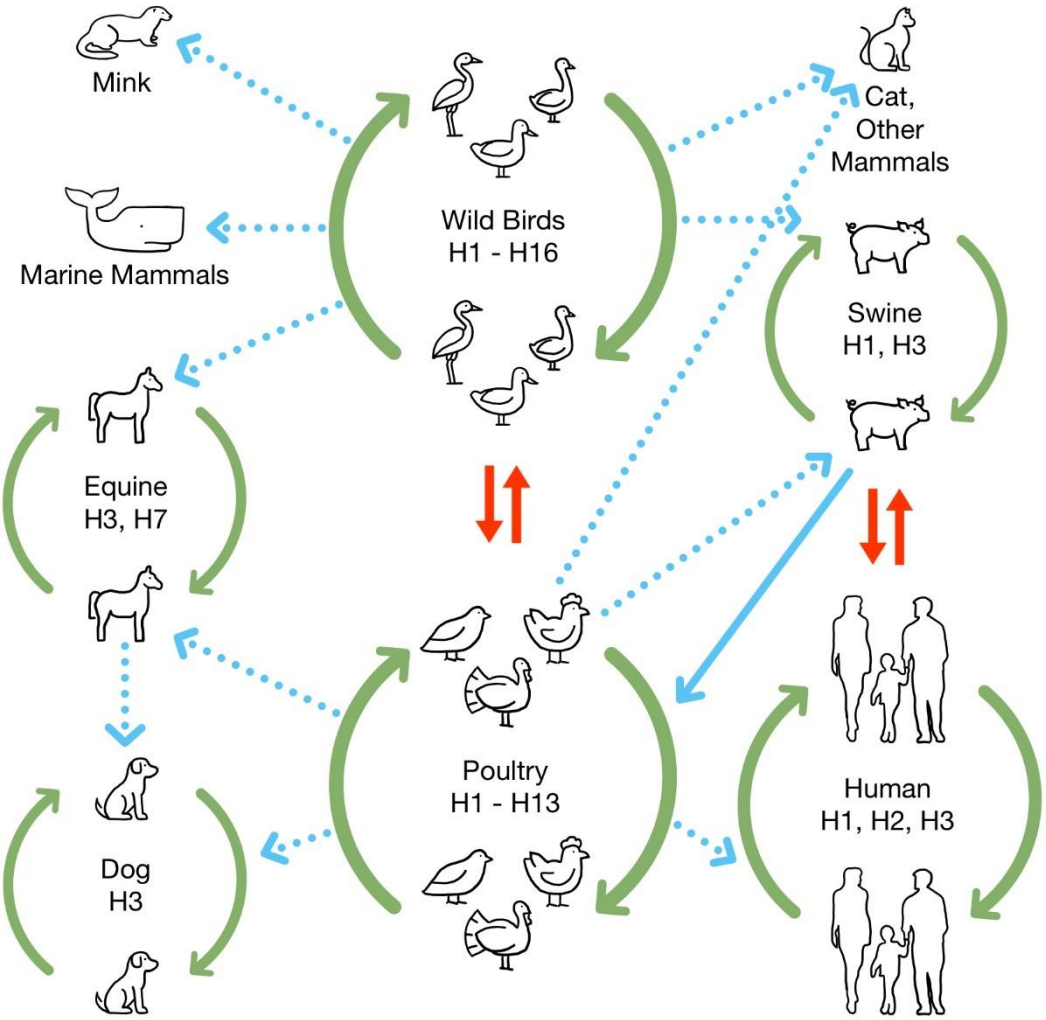

Figure 2: Influenza A virus transmission across species [25]

2.2. Geographical occurrence

Swine influenza is present worldwide with a variable prevalence and types of strains [26]. While swine influenza once has been regarded as a seasonal disease, meaning it primarily occurred during winter and spring, this may no longer be the case due to the highly concentrated raising models in the swine industry [27].

The disease is common in Europe, North and South America, and regions of Africa and Asia [26]. Among the subtypes (HxNy) of IAV, the most common ones in swine are H1N1, H1N2 and H3N2. They are widespread and enzootic in pig producing areas across Western Europe [28]. Nevertheless, their origin, genetic background and antigenic properties vary significantly depending on the region [14].

2.3. History

Historically, IAV in swine first emerged alongside the disastrous human influenza pandemic, referred to as the Spanish flu in 1918. This "classic human H1N1 virus" was isolated first from pigs in 1930 [29, 30]. It was transmitted from humans to pigs and persisted in the porcine population in Europe until the 1970s. During this time, it was replaced by a new H1N1 virus originating from an avian host, which has maintained a widespread presence among European swine populations to this day.

The porcine subtype H3N2 emerged in 1984 through reassortment of this “avian-like” H1N1 virus with a human seasonal H3N2 virus. H3N2 has since emerged as endemic in some European countries, including Germany [31].

The porcine subtype H3N2 reassorted with a human seasonal H1N1 virus in 1994, resulting in the H1N2 subtype in pigs, commonly known as "human-like" H1N2 [32].

The H3N1 virus was initially identified in pigs in the United States in 2004, originating from a combination of classical H1N1 and triple-reassortant H3N2 [33].

Another subtype, the human pandemic H1N1 virus, entered the scene in 2009. This strain likely arose from multiple reassortment events, possibly occurring in the Americas. Since then, it has firmly entrenched itself as a seasonal H1N1 virus within the human population. Similar to the transmission dynamics observed with the H1N1 virus of the Spanish flu, there appears a reverse zoonotic transmission, indicating that the virus was passed from humans to pigs and has later disseminated extensively within porcine populations (*Figure 3*). It now plays a significant role in reassortments with the three older porcine IAV lineages in Europe [31, 34].

The swine-adapted reassortant of the human pandemic H1N1 virus, known as pandemic H1N2, was shortly thereafter detected in Germany. Until that point, isolated influenza outbreaks had been observed in different geographic regions like Europe, the Americas, and Asia. With the emergence of the pandemic influenza strain, the genetic isolation between these regions was effectively broken. Since then, pandemic influenza has circulated globally in swine populations with significant genetic diversity and dynamic evolution [35].
In 2014, a triple-reassortment between porcine and human influenza viruses emerged, giving rise to a new H3huN2 virus [36].

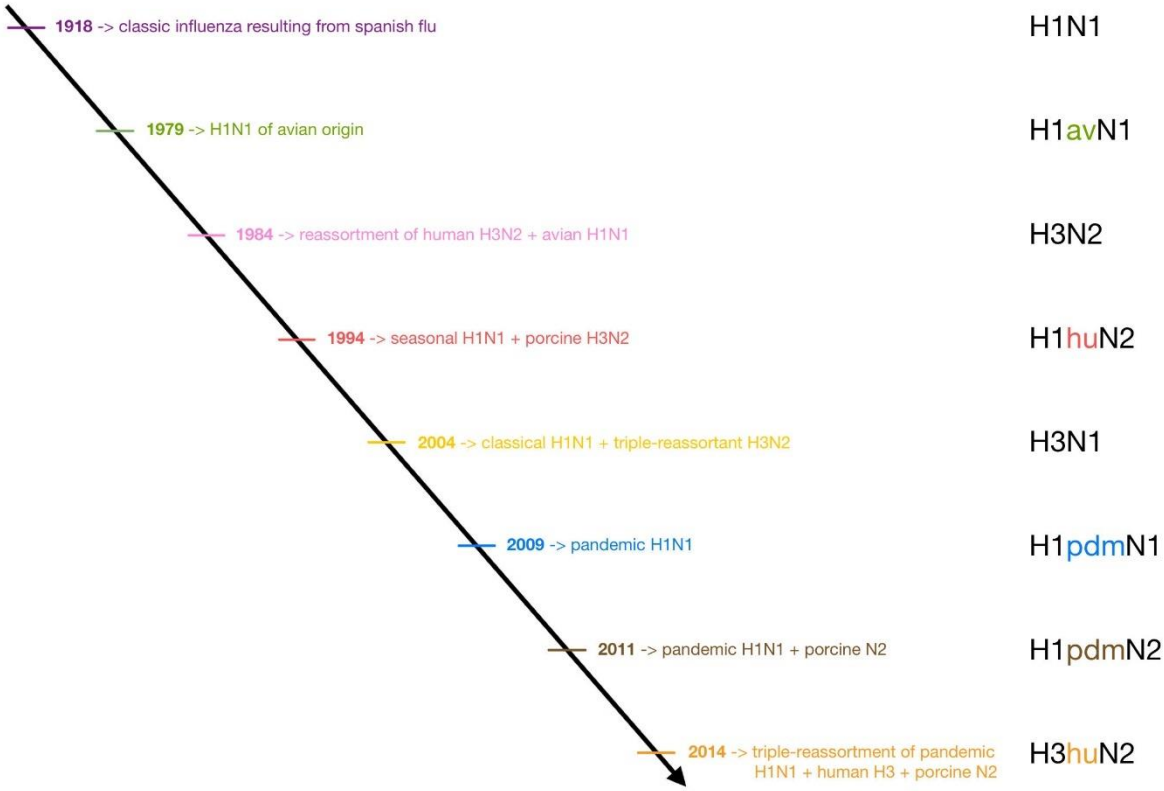

Figure 3: Origin and emergence of the currently circulating porcine influenza A virus reassortments in German swine populations [32, 33, 37]

3. The importance of "mixing vessel"

The biggest challenge in combating influenza is the virus's remarkable ability to mutate and, in this context, the domestic pig population plays a leading role in the influenza epidemiology [19].

The host specificity of IAV hinges primarily on the interaction between viral surface proteins and host cell surface structures, commonly referred to as receptors. Additionally, the efficacy of all subsequent replication processes post-infection may also influence tropism. Viral mechanisms, including protein structures, are intricately tailored to optimize interaction with the host cell [38]. The affinity of HA for sialic acid molecules on glycoproteins of the host cell membrane emerges as a pivotal determinant [39].

As previously mentioned, swIAV subtypes H1N1, H1N2, and H3N2 circulate worldwide and exhibit seasonal patterns, leading to respiratory illness in pigs and indirectly affecting reproduction. Consequently, swIAV negatively impacts animal welfare and inflicts economic losses on the pig industry [5, 40]. Co-infections in pigs with IAV of porcine, human or avian origin can create novel reassortant swIAV, potentially possessing a high zoonotic trait or even pandemic characteristics [41, 42]. However, other species, such as equine, canine, bovine and bat influenza, are of low to negligible zoonotic potential [43].

Due to their receptor configuration, pigs were deemed as "mixing vessel" for the emergence of novel influenza viruses through genetic reassortment in them (*Figure 4*) [42]. This issue stems partly from their presence in the porcine respiratory tract, along with the widespread and concentrated distribution of the two receptors that facilitate viral entry in avian and mammalian IAV [44–46]. A pivotal factor in influenza infection is the availability of virus receptors on susceptible host cells to which the viral HA can bind [47]. Avian viruses have a preference for binding to SA–α2,3–galactose located mostly in the intestinal tract, while human strains preferentially bind to SA–α2,6–galactose which are located in the respiratory tract [43]. Both receptors are expressed by the airway epithelia of the respiratory tract of pigs, although more SA–α2,3–galactose than SA–α2,6–galactose receptors are present.

Consequently, pigs are susceptible to influenza viruses adapted to either birds or humans and can act as intermediate hosts following cross-species transmission [47]. This poses a constant challenge not only concerning the swine population, but also the public health dimensions must be taken into consideration [19].

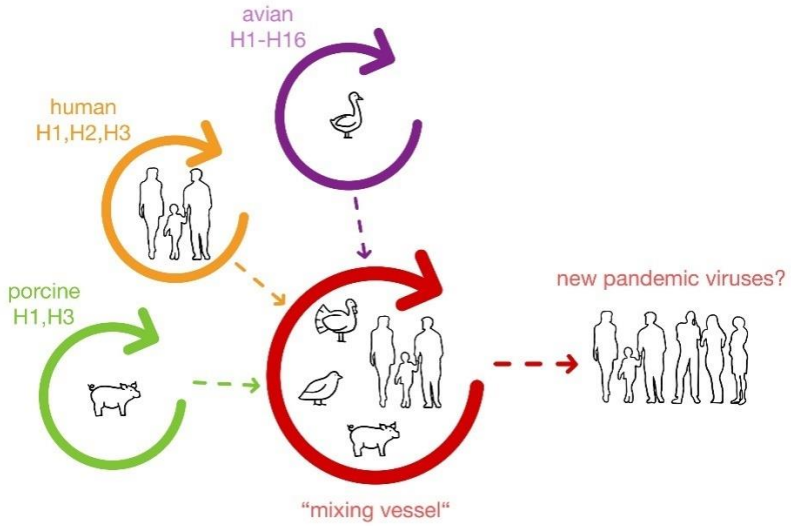

Figure 4: Potential "mixing vessel" host species presenting sialic acid receptors for human- and avian-adapted IAV in their respiratory tracts [34]

3.1. Public health

Variants of newly emerging or circulating IAVs pose recurring global health threats to animals and humans. A significant global concern is that zoonotic viruses could develop mutations in animal or human hosts, enhancing their ability to transmit efficiently from animals to humans or persistently between humans. Pigs and poultry are the primary sources of IAV infections in humans [48].

Transmission of IAV from swine to humans occurs infrequently and mainly sporadically, unlike the more frequent spill-over events from birds to humans. For zoonotic cross-species transmission between swine and humans to happen, it typically demands highly susceptible individuals to be exposed to a high virus load [34]. IAV strains originally adapted to another host do mostly not represent an efficiently transmission from person to person, meaning that even successful initial infection of a new host results in only a few cases in an efficient infection [48].

Individuals in close contact with domestic poultry or pigs are usually the first to be affected by infection with non-human IAV, for instance, at agricultural fairs, live animal markets, slaughterhouses or in pig holdings [34, 43, 48]. Additionally, the increasing interaction between livestock and wild birds offer a further important source. Properly handled and thoroughly cooked meat does not serve as a source of infection [48].

Although humans often have partial immunity to severe influenza symptoms through prior infections or IAV vaccination, the absence of immunity to antigenically new HA and NA

variants can lead to significant virus replication and rapid spread within the population. In some cases, an excessive immune reaction to the new virus can cause a “cytokine storm,” leading to severe illness and increased mortality [43].

Taking this into consideration, it is imperative to consistently monitor the processes of viral adaptation and the zoonotic potential of swIAV.

4. Pathogenesis

Swine influenza is a significant respiratory disease affecting pigs, generally entering a herd through an infected animal [41]. The disease tends to occur throughout the year, but it is more frequent in the colder months [37]. It is important to mention that today, classical influenza occurs much less frequently than in the past. Nowadays, endemic forms with nonspecific symptoms prevail, where reproductive problems and reduced weight gain are often the only noticeable signs [34, 49, 50].

In the case of classical strains, newly infected herds are often affected by a high number of cases, with morbidity rates approaching 100%, while mortality rates generally remain low, typically below 1% to 4%. While many cases remain subclinical in herds with enzootic infections, about 25% to 30% of pigs may display typical signs of influenza. The incubation period is brief, typically lasting between one to three days, and most animals recover within three to seven days if no secondary bacterial infections or other complications arise [41].

The swIAV replication is confined to epithelial cells lining both the lower and upper respiratory tracts of pigs, encompassing the nasal mucosa, ethmoid, tonsils, trachea, and lungs. Excretion and transmission of the virus primarily happen through the respiratory pathway [27, 51]. It is improbable for the virus to disseminate beyond the respiratory tract, typically without any viremia [40].

Transmission of the swine influenza virus can occur through droplets and aerosols generated by coughing and sneezing, as well as through direct contact between infected and uninfected animals. Direct contact via the nasopharyngeal route serves as the primary mode of transmission, especially through contact of mucus or nose-to-nose interaction.

The virus is expelled through nasal secretions during the acute febrile stage and disseminated through droplets or aerosols. Pigs may begin shedding the virus within 24 hours of infection, with shedding typically ceasing within 7 to 10 days post infection. Close contact and confined environments facilitate transmission, enabling the virus to spread rapidly through a herd, infecting all pigs within days [41].

Pigs raised in concentrated feeding operations increase the risk of transmission, while transmission can also occur through humans and wild animals, potentially spreading the disease from infected to uninfected farms [27].

5. Disease presentation

5.1. Clinical signs

As a highly contagious viral infection that spreads rapidly among pigs, swine influenza has previously caused acute outbreaks affecting large portions of herds simultaneously [26]. In the past, particularly in immunologically naive populations, it would present as a sudden-onset disease, yet it often resolved due to its self-limiting nature [52].

However, following the emergence of pandemic strains in 2009, the dynamics of the disease changed. The swIAV strains now circulate more persistently within herds, spreading throughout the year and causing more nonspecific signs which differs from those associated with classical influenza [34]. This endemic presence has led to a prevalence of milder cases with respiratory issues across different age group. This situation allows the virus to spread insidiously, often without clear signs of an outbreak [50, 53, 54]. However, severe cases with significant animal losses are occasionally observed [55]. Additionally, these strains can exacerbate reproductive issues, further impacting the affected herds [49].

The classical acute outbreaks were usually limited to fully susceptible, seronegative pigs, whether they are unprotected nursery pigs or older pigs. They are marked by clinically typical signs [52]. As an acute upper respiratory disease, it presents with signs including high fever (up to 42°C), lethargy, huddling, anorexia, and weight loss. Infected pigs may also exhibit coughing, sneezing, nasal and ocular discharge, conjunctivitis, tachypnoea, and laboured breathing [40, 52, 56]. The cough typically develops a couple of days following the onset of illness, coinciding with the decline in fever [40]. Laboured abdominal breathing and dyspnoea are particularly attributes of the disease [52].

In more severe cases, complications such as pulmonary oedema or bronchopneumonia can occur, potentially leading to death [41]. In some herds, abortions may also be seen [57].

The dose of infection and the route of exposure are crucial in determining the development of inflammatory processes and clinical outcomes [58]. Along with the immune status, factors such as age, infection pressure, climatic conditions, housing, and concurrent infections significantly influence the clinical course of swIAV infection [59].

Furthermore, the severity of clinical signs can be worsened by secondary bacterial or viral infections and coexisting illnesses. Secondary bacterial infections caused by *Actinobacillus pleuropneumoniae*, *Mycoplasma hyopneumoniae, Haemophilus parasuis, Pasteurella multocida* or *Streptococcus suis* type 2 may contribute significantly. Additionally, distinct respiratory viruses, including porcine respiratory coronavirus (PRCV) and *Betaarterivirus*

europensis and *Betaarterivirus americense* responsible for porcine reproductive and respiratory syndrome (PRRS), often infect pigs of the same age group as those affected by swIAV [60]. Among these pathogens, PRRS, *M. hyopneumoniae*, and swIAV are most commonly associated in 10 to 22 week old pigs with the multifactorial "porcine respiratory disease complex" (PRDC) resulting in pneumonia development [61].

Since swIAV is frequent association with PRDC, the decline in performance and animal well-being caused by this virus is intensified by the presence of pathogenic co-infections. In the United States, the estimated costs incurred per finishing pig reached $10 when accounting for PRDC co-infections, representing a significant loss in revenue for producers within the industry [62]. Viral infections like swIAV significantly affect farm profitability, with economic consequences such as reduced weight gain in fattening pigs, due to decreased feed conversion efficiency and slower overall growth rates, and lower reproductive performance in breeding sows [27, 62]. The 2009 H1N1 pandemic underscores the significant financial impact of swIAV on the pork industry. Beyond the direct financial implications, prevalent public misconceptions about the safety of pork consumption, combined with fears regarding ongoing transmission from pigs to humans, severely affected the U.S. pork industry. The estimated final losses in the U.S. alone exceeded $1.3 billion USD due to these factors [62].

5.2. Pathological findings

5.2.1. Macroscopic lesions

Like the clinical presentation, lung lesions may be mild or inconspicuous. If they are present on postmortem examination, the most frequent macroscopic demonstration of an influenza infection is cranioventral bronchopneumonia. This outcome would be anticipated because the virus primarily reaches the lungs through the airways, rather than via viremia. The virus predominantly targets the epithelial cells throughout the respiratory tract, extending from the nasal mucosa to the alveoli. It has also been identified in the glandular epithelial cells of the larger airways [40].

The mucosa of the upper respiratory tract is congested, and the mediastinal and bronchial lymph nodes are increased in size and oedematous. Despite the virus infecting the epithelial lining of these upper airways, visible necrosis does not typically occur [63, 64].

The affected lungs typically show sharply demarcated areas of hyperaemia and consolidation, with a firm texture and a characteristic purple-red appearance. In cases of

milder infection, small clusters are observed in the cranial and middle lung lobes in the cranioventral areas of the caudal and accessory lobes [40]. Multifocal to coalescing regions of consolidation are present, often accompanied by inflammatory exudates within the airways, and interlobular oedema may also be observed (*Figure 5*) [65].

In more severe cases, a larger, typically more ventral area of the lung is affected, often involving the cranial and middle lobes as well as the cranioventral portions of the caudal lobe, with up to 40% of the total lung volume becoming consolidated [40]. In naturally arising influenza, these lesions can become aggravated or obscured by simultaneous bacterial bronchopneumonia, leading to more extensive damage [40, 66].

In rarer instances, severe acute infections manifest as diffusely congested lungs, marked by pronounced interlobular oedema and spacious foam in the bronchi and trachea. These cases likely reflect an intense cytokine response, which masks the cranioventral lobular consolidation with more diffuse interstitial pneumonia and oedema [40].

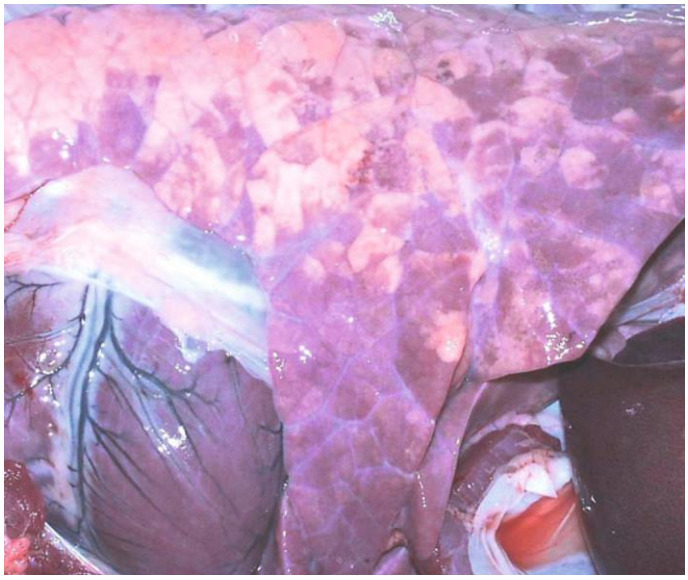

Figure 5: Field case of swine influenza in a grow-to-finish pig, where extensive lobular and sublobular consolidation is observed, involving the cranioventral lung [67]

5.2.2. Microscopic lesions

The key microscopic lesion, which is usually considered pathognomonic for swIAV infection in pigs, is necrotizing bronchitis and bronchiolitis. Additionally, interstitial pneumonia is also observed, with varying degrees of severity [40]. These characteristic lesions typically

manifest a few days after the virus has been eliminated from the pig, particularly in instances where coinfections are present [68].

The initial immune response involves neutrophil infiltration, with neutrophils migrating through the airway epithelium and accumulating in alveolar capillaries. The alveolar walls become thickened due to vascular congestion and lymphatic dilation, with possible subtle epithelial degeneration in smaller bronchioles.

By 24 hours PI, neutrophils begin to accumulate around the bronchioles, and light, loose lymphocytic cuffs appear around the airways.

Necrosis and sloughing of airway epithelial cells become evident by 24 to 48 hours PI, with further neutrophil accumulation (*Figure 6*). The affected epithelial layers may appear swollen, and alveolar walls show diffuse thickening. Some infected cells in alveoli, mainly macrophage and swollen pneumocytes, may also be identified.

By 48 hours post-infection, the affected airways are characterized by flattened epithelial layers. The neutrophils that previously populated the luminal debris have either been replaced or are now accompanied by macrophages. Additionally, lymphocyte infiltration around the airways and nearby blood vessels increases, indicating a more pronounced immune response [40]. The neutrophils lead to airway obstruction and could play a role in lung injury through the secretion of their enzymes. Within a few days, lymphocytic accumulation around the bronchi and blood vessels becomes prominent [64, 69].

By 72 hours PI, some airways continue to necrotize, while others begin to repair, with hyperplastic epithelium and lymphocytic cuffs forming around bronchioles. Leukocyte populations shift towards mononuclear cells and numerous scattered infected cells are detected in the alveoli, often limited to certain lobules.

By 96 hours PI, most airways enter a reparative phase, with inflammation resolving. The lungs generally regain normal function within two weeks, depending on the extent of the damage. In severe cases, proliferation of fibroblasts may result in the formation of endobronchial polyps or incomplete splitting of repairing airways. The trachea shows minimal damage with few infected cells, and the nasal epithelium remains mostly unaffected despite heavy viral shedding. Lung lobules in the same section can vary in involvement, with some unaffected and others severely impacted, likely due to uneven virus distribution in the respiratory tract [40, 67].

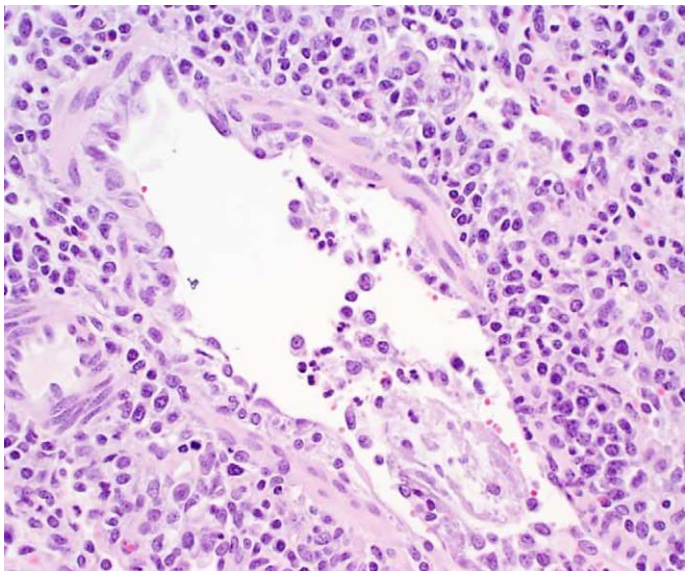

Figure 6: Acute phase of swIAV in pig lung with necrosis and sloughing of bronchiolar epithelium, neutrophil clusters in lumen, and light peribronchiolar lymphocyte infiltration (Haematoxylin eosin stain) [40]

6. Diagnostic evaluation

Through reassortment and mutation, the ecology of IAV has become more complex, as have diagnostic methods and sample types used for viral detection [70].

In case of a sudden onset of severe respiratory disease involving many pigs, especially during the winter months, swIAV should be suspected [71]. It lacks specific pathognomonic signs, making it essential to differentiate it from other respiratory diseases in pigs that present with similar clinical and pathological features [27].

Accurate diagnosis of uncomplicated influenza infections requires ruling out other conditions, such as bacterial and viral infections [71], the specifics of which were already detailed in the previous section on clinical signs. These diseases often co-occur with swIAV, especially in outbreaks characterized by significant mortality [40].

The most prevalent techniques for the detection of swIAV include reverse transcription–polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), the haemagglutination inhibition (HI) test, and the neuraminidase inhibition (NAI) test [70].

6.1. Direct virus detection

To effectively detect and identify pathogens, it is crucial to acquire tracheal, lung and nasal swabs within 24 to 72 hours following the onset of clinical symptoms. As an alternative approach, oral fluids can be obtained from cotton ropes placed in the pig enclosure, serving as a valuable group or population sample [42].

Oral fluids have become the preferred sample type due to their ease of collection and their ability to better represent large animal groups [72]. However, they may harbour inhibitors that can interfere with RT-PCR results [73]. On the other hand, nasal swabs tend to contain higher virus loads, making them more effective for sequencing and virus isolation [74].

For the isolation of viruses, the standard practices involve the use of embryonic chicken eggs and various cell cultures. Conventional approaches for classifying influenza viruses, focus on the detection of NA and HA. This process includes conducting HI and NAI tests on the isolated viruses [42].

The most rapid and precise technique for detecting viral RNA and identifying subtypes of the swIAV is through PCR analysis, which has recently been established as the preferred method for diagnosing swIAV infections, thanks to advancements in molecular diagnostics. This method specifically aims at M protein, HA, NA and NP. Furthermore, a range of commercially available test kits are commonly employed in this context to facilitate testing

[70]. RT-PCR is noted for its specificity, sensitivity, and cost-effectiveness in providing quick diagnoses [42].

The availability of advanced diagnostic kits for detecting viral RNA and verifying swIAV infections offers significant benefits, particularly because they include internal control standards and positive reference samples tailored for the relevant serotypes. The increased sensitivity of RT-PCR requires careful consideration, as it has the ability to detect viral RNA even when no infectious virus is present. Therefore, findings with low detection thresholds should be interpreted with caution, as they may not accurately reflect an active infection. The detection and differentiation of subtype strains is facilitated by a multiplex, one-step qRT-PCR kit, which enables early identification and contributes to minimize the transmission of the virus. Both kits exhibit high specificity and sensitivity [70].

6.2. Serological techniques

The HI test is regarded as the gold standard serological test for detecting swIAV. This test, performed on paired serum samples, specifically targets the HA subtype. Preferably, serum samples are obtained 10 to 21 days apart to accurately track the changes in antibody titers effectively [14]. Circulating antibodies typically become detectable within 10 to 14 days after infection [75].

Apart from the HI test, other serological methods employed for detection include the agar gel immunodiffusion assay, indirect fluorescent antibody method, virus neutralization, and ELISA. Given the increasing antigenic diversity in swIAV strains, there has been a growing shift towards the implementation of commercially available ELISAs not limited to particular subtypes. These ELISAs offer broader diagnostic capabilities, addressing the limitations posed by the necessity to include multiple hemagglutinin subtypes in HI assays [14].

The swIAV antibodies can be detected in serum or plasma samples using a blocking ELISA that targets the conserved influenza NP. This method offers significantly higher sensitivity and specificity compared to competitive ELISAs, which are generally not recommended for detecting antibodies against current swIAV strains [76, 77].

These commercial quantitative indirect ELISAs can identify natural virus infections and monitor responses to killed vaccines. Results have demonstrated perfect sensitivity based on field samples and excellent specificity in non-vaccinated pigs. However, it is not appropriate for confirming protection against infection [77]. In addition ELISA test kits are utilized to identify not only post-infectious antibodies but also maternally acquired antibodies and those generated following vaccination [78].

For herd surveys, both the HI and ELISA are commonly employed to assess the prevalence of antibodies across the herd [27].

The presence of vaccines and active endemic infections may limit the effectiveness of serological tests, making careful interpretation in the context of herd-specific symptoms and characteristics essential. Additionally, serologic testing is complicated by the presence of several swIAV subtypes within a group of pigs, and many serologic tests do not cross-react sufficiently to detect antibodies of all swIAV subtypes. Therefore, subtyping the virus through PCR, genetic sequencing, or advanced serologic methods is crucial for more precise interventions [75, 79].

7. Treatment

There is no specific treatment available for swIAV, as it is a viral disease, and treatment is generally unnecessary unless secondary infections are present. Pigs usually recover fully within a week, with supportive care being the main approach. Administering anti-inflammatory drugs, through feed or water, can aid in accelerating recovery [80].

However, when secondary infections occur, rapid administration of appropriate antibiotics is crucial to prevent significant losses. Effective management practices during an outbreak are essential to minimize the disease's impact [81, 82].

During an swIAV outbreak, pigs may experience slowed growth and will not be fit for slaughter while ill. To manage the disease, avoiding overcrowding and, in some cases, reducing slaughter weight after recovery may be necessary. Key measures include maintaining a clean, dry, and dust-free environment, ensuring that sick pigs are separated from healthy ones, and providing adequate rest for those affected [27].

8. Prevention and Control

8.1. Risk factors

To eliminate the endemic circulation of viruses within a herd, strategies must be implemented to break the chains of infection. Numerous studies explore risk factors associated with persistent or recurring influenza infections at the herd level.

Husbandry and management practices are critical in determining the risk of swIAV infections on pig farms. The most vulnerable stages for pigs occur shortly after birth and post-weaning, making it crucial to ensure good health and appetite in weaned pigs, as this supports long-term growth and development. Weaning groups free from swIAV infection offer significant benefits to swine producers by improving both animal health and productivity while reducing the risk of transmitting the virus to other locations and the public [83].

Key factors include larger farm sizes and overcrowding [84–88]. Farms with a higher number of finishers per water source tend to show elevated rates of swIAV positivity. This is likely due to increased direct and indirect contact between animals, along with higher social stress, which can suppress the immune system [84]. Implementing stress-reducing strategies, such as maintaining appropriate room temperatures and utilizing straw yards or extensive outdoor housing systems, as well as appropriate feed adjustments has been shown to decrease infection risks [84, 88, 89]. Poor management practices, such as the absence of all-in, all-out management in fattening rooms, further increase the risk of infection [84, 90]. Higher replacement rates in gestation units and certain farming systems, particularly farrow-to-finish and breeding herds, are also associated with an increased risk of swIAV infection compared to finisher farms. To lower weaner prevalence, it is important to maintain suckling periods of less than 28 days and ensure the presence of fully slatted floors in pens [90, 91].

Effective measures to reduce swIAV prevalence include thoroughly testing replacement gilts for shedding of this virus before introducing them to sow herds and designing pens with solid barriers to reduce contact between animals from separate groups [90]. Such close contact can facilitate the spread of airborne pathogens, making solid partitions an important preventative measure [92]. Acclimatization units for gilts, which are transition areas isolated from gestation and maternity sections, effectively control influenza virus in breeding herds. They allow gilts to adjust to farm pathogens and recover from infections before joining the main breeding areas. Unlike gilts, older sows typically show higher immunity levels due to prolonged exposure [93].

Another important factor IS close human-pig interactions, particularly involving individuals exhibiting influenza-like symptoms. Uncontrolled access to the farm by vehicles, people, and wild animals are also critical factors that can facilitate the introduction of the disease [87, 94]. To reduce these risks, essential biosecurity practices include isolating sick animals in separate buildings and restricting access to the farm [84, 90].

Thorough hygiene is essential, ensuring that pens and corridors are thoroughly cleaned and disinfected after use. Changing clothing and maintaining hand hygiene are crucial, as well as using separate equipment for each barn and age group. Critical points that increase the risk of infection include intersections of corridors and air intake routes [89].

Proximity to other farms, mixing of livestock species, and the absence of bird-proof nets further enable virus transmission. Wild birds, especially waterfowl, serve as reservoirs, potentially transmitting viruses to pigs either through direct shedding or as mechanical carriers [89, 93, 95].

Environmental factors also play a substantial role in the risk of swIAV infections. High pig farm density is a significant risk factor, as it correlates with influenza infections from both human and avian strains in pigs. Other environmental and meteorological factors, including poultry density, human population density, rainfall, temperature, and proximity to bodies of water, are also associated with influenza transmission, particularly from avian sources [96, 97]. Seasonality is a key driver of swine influenza outbreaks, with the virus being more prevalent during colder months. Transmission becomes more effective during this period due to lower temperatures and decreased ventilation in indoor herds [84]. The latter promoting higher air humidity and harmful gas concentrations leaving the respiratory tract more prone to infections [98]. In spring and autumn, temperature fluctuations further weaken the immune system. While swIAV can persist throughout the year due to the continuous presence of susceptible pigs, colder months typically witness higher within-herd prevalence and an increased likelihood of detection [84].

By integrating effective management strategies, strong biosecurity measures, and careful monitoring of environmental factors, the spread of SIV on pig farms can be sustainably controlled, safeguarding both animal health and farm economic stability.

8.2. Vaccination

In swine influenza management, vaccination of sows with commercial or autologous adjuvanted whole inactivated vaccines (WIV) remains the cornerstone alongside biosecurity

measures and herd management [7, 99]. Due to their segmented RNA genome and error-prone replication, IAVs evolve rapidly through genetic drift and shift, adapting to new hosts and evading immunity. The year-round circulation in commercial pig farms further accelerates the evolution and transmission of zoonotic strains, complicating vaccination efforts, as new variants often emerge that evade innate, natural, and vaccine-induced immunity, thereby reducing vaccine effectiveness [34, 100].

Swine immune responses rely on both humoral and cellular mechanisms, with antibodies against the HA protein being critical for preventing infection and eliminating the virus. Antibodies targeting NA also help limit viral spread. However, the effectiveness of these antibody responses is influenced by factors such as viral dose and subtype. When neutralizing antibodies, some of the antibodies to the HA, are well-matched to the circulating virus, they effectively inhibit the virus's ability to bind to sialic acid receptors on host cells, which in turn reduces the viral load in the lungs. The degree of cross-protection offered by these antibodies' hinges on the genetic similarity and specific epitope matching of HA proteins across different viral strains [6].

The currently used vaccines for swine influenza in Germany include Respiporc Flu 3 and Respiporc FLUpan H1N1, both manufactured by "Ceva Santé Animale" [50, 99]. Respiporc Flu 3, as a trivalent heterologous vaccine, targets swine influenza subtypes H1N1, H3N2, and H1N2. Respiporc FLUpan H1N1, as a monovalent vaccine, is aimed at protecting pigs from the pandemic H1N1 strain of swine influenza [99, 101, 102]. Vaccine efficacy is influenced by factors such as the genetic similarity between the circulating virus and the vaccine strain, the immune response triggered by the vaccine, the amount of antigen included, and the use of adjuvants. The accuracy of the HA match between vaccine and field strains is particularly vital, as inactivated vaccines primarily stimulate neutralizing antibodies to this protein [6].

The most commercial swIAV vaccines are WIV vaccines with adjuvants that induce strain-specific humoral responses. Adjuvants, along with the frequent re-vaccinations every 4 to 6 months associated with Respiporc Flu 3, may enhance the breadth of antibody and T cell responses [99, 101]. For Respiporc FLUpan H1N1 the immunity lasts for 3 months and no revaccination schedule is proposed [102]. It is important to note that the onset of the immunity typically begins 7 days after the first vaccination and that the second shot has to follow after three weeks to ensure a primary immunity [101, 102]. Routine pre-farrow booster vaccination with Respiporc Flu 3, administered 14 days prior to farrowing, results

in higher and longer-lasting maternal antibody levels, providing colostral immunity that protects piglets for a minimum of 33 days after birth and during their nursery phase against clinical symptoms, but not against the initial viral infection [101]. Usually, maternal antibodies from vaccination typically persist for about 5 to 8 weeks following birth [101, 102]. Additionally, vaccinating sows is advantageous for preventing fever-related abortions [103]. While vaccinating feeder pigs is relatively uncommon and can be challenging to coordinate with sow vaccination due to extended passive immunity potentially hindering the effectiveness of piglet vaccination, it may still be beneficial in herds experiencing influenza issues in growers and finishers. Further complications are associated with vaccinating piglets at due to their movement between finishing and breeding farms. The resistance to swIAV in piglets provides no advantage to the breeder, who sell these piglets shortly after weaning, while growers primarily gain from their vaccination. However, breeders should ideally vaccinate to prevent the spread of swIAV between farms. Otherwise, some piglets may arrive already infected, which ensures that susceptible pigs persist within the production chain [62].

Newborn piglets rely on maternal antibodies for protection, as they are born without any due to the inability of these antibodies to cross the placenta. Maternal IgA, IgG, and IgM antibodies are passed through colostrum within the first 36 hours after birth [6]. In particular, antibodies of the IgA type are important for mucosa-associated protection against reinfection [104]. However, in swine herds with ongoing swIAV infections, piglets with maternally derived antibodies can act as asymptomatic amplifiers of the virus. While maternal antibodies provide systemic protection, they do not offer complete immunity, allowing for the possibility of infection without generating measurable active humoral immunity [99]. These maternal antibodies, while protective, may impede the development of active immunity in piglets' post-vaccination and reduce the effectiveness of WIV vaccines. Typically, maternally derived antibodies from vaccination last approximately 5 to 8 weeks after birth. In certain cases, where sows have multiple antigen exposures the antibodies transferred to piglets may last until 12 weeks of age. Consequently, active immunization is often delayed until the fattening phase, raising the risk of an immunological gap during weaning [101, 102]. Piglets with maternal antibodies show slower growth after their initial exposure to swIAV compared to those without maternal antibodies, although they tend to experience better growth after subsequent exposures. If maternal antibodies do not match well the strain, there is a risk of vaccine-associated enhanced respiratory disease (VAERD), complicating immune responses [6].

9. Clinical significance on German pig farms

The swIAV has become increasingly significant in Germany in recent years. While outbreaks were once isolated incidents, the virus now spreads insidiously and remains persistently endemic in pig populations over extended periods. Traditional classical flu infections have diminished as the dynamics of the disease have shifted following the emergence of pandemic strains in 2009 [5].

Classical outbreaks typically manifest with acute and intense symptoms, characterized by high fever, apathy, reduced feed intake, and severe pneumonia accompanied by coughing. Occasionally, these classical cases may result in sudden deaths or fever-induced abortions; however, this severe presentation has become less common [40, 41, 57].

In contrast, today's influenza viruses now circulate endemically year-round, resulting in recurrent waves of infection. The clinical presentation is often much less specific than what is typically seen with classical influenza, leading to many infections going unrecognized and persisting within herds for extended periods [50, 53, 54]. The prevalence of pandemic strains in swine populations has increased in recent years, while the presence of the classical strains has declined (*Figure 7*).

The pandemic swIAV's subtypes can cause fever and respiratory illnesses across various age groups, and they particularly impair reproductive performance, resulting in abortions at all gestational stages and reduced litter quality in infected sows, along with increased cases of MMA (mastitis, metritis, agalactia) and higher rates of underdeveloped piglets [49, 105]. Further symptoms of influenza in sows may include lethargy, reduced appetite, respiratory issues, high return-to-estrus rates, and unexplained abortions at various pregnancy stages, often resulting in weaker piglets and lower litter quality [49]. These issues often arise without an apparent cause, affecting sows across all stages of pregnancy. However, the timing of farrowing does not deviate from the usual 115 day [49, 106].

Pandemic influenza viruses significantly suppress the immune system, weakening resistance to other pathogens [60, 61]. The persistent presence of swIAV exacerbates secondary bacterial and viral infections, often resulting in severe illness, increased piglet mortality, and impaired immunity, leaving animals susceptible to recurring infections. Secondary infections often manifest subtly, with signs like increased antibiotic use and reduced growth rates, contributing to uneven waves of disease and associated losses [50]. This impacts the production chain from piglet rearing to slaughter. Environmental stressors further contribute to respiratory problems, exacerbated by seasonal weather changes [96, 97].

The economic impact is substantial, with high treatment and feed costs, along with increased effort and financial losses across production stages. Respiratory diseases reduce growth performance and feed efficiency, extend fattening periods, cause uneven growth within groups and raise maintenance costs. Although treatment and medication costs are high, investing in animal health can be profitable in the long term, as healthier sows produce more piglets and improve overall profitability [49, 50, 88].

The “Ceva Santé Animale” dynamic flu map illustrates the prevalence of swine flu subtypes across Europe. In Germany, data from January 2022 till November 2024 (*Figure 7*) show that H1avN1 is the most common subtype, followed by H1huN2 and H1avN2. The fourth most common subtype is H1pdmN1, followed by H1huN1 in fifth place and H1pdmN2 in sixth. Subtypes like H3N1 and H3N2 are rarely detected. Cases involving the pandemic strain H1pdmN1, which emerged from humans in 2009, have increased in recent years. Its share of the subtypes occurring has already risen from nearly 5,8 % in 2022 to 14,8 % in 2024 [107].

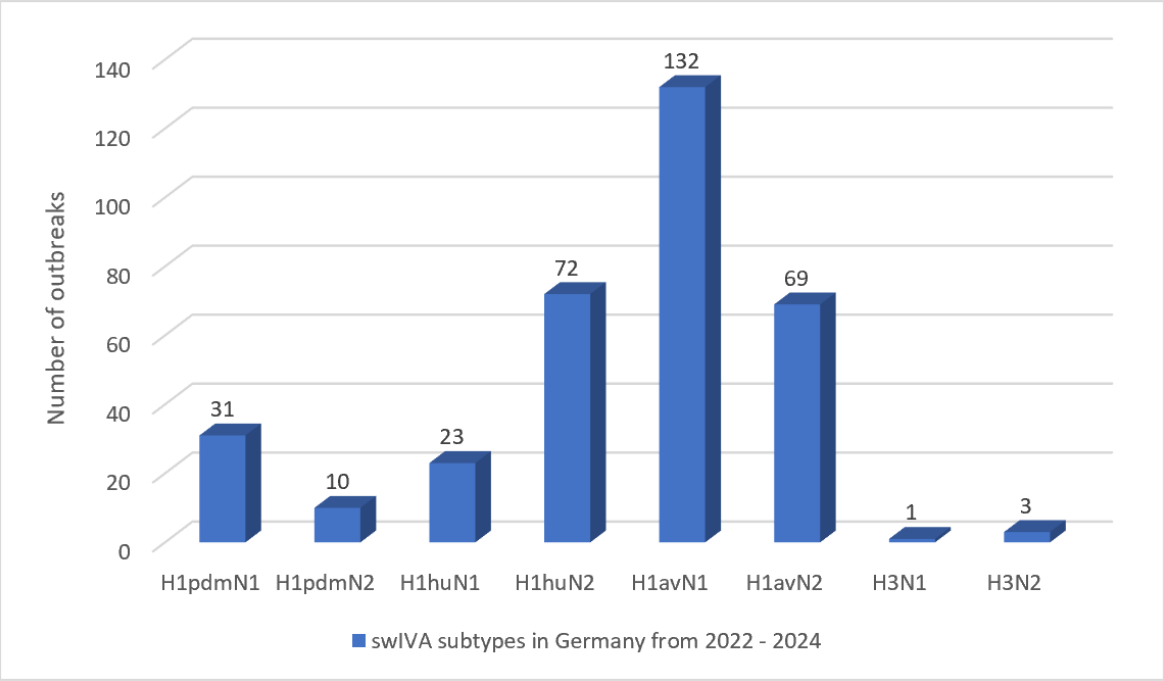

Figure 7: Occurrence of different swIAV subtypes in Germany from 2022 to 2024 [107]

After several years of significant declines, the pig population in Germany appears to be stabilizing, even as the number of pig farming operations continues to decrease. This trend is confirmed by the latest livestock count from the Federal Statistical Office Germany,

conducted in 2024, which reports 15,700 farms, which are 600 fewer than the previous year. There are currently 20.9 million pigs in Germany, which is nearly unchanged from the previous year, with a slight reduction of 1,200 animals. The trend toward larger operations continues, with an average farm now housing approximately 1,300 pigs in 2024, compared to 1,000 in 2014 [108]. However, the industry still faces significant challenges. Despite currently favourable selling prices due to reduced supply, structural issues persist. High production costs compared to international standards, inflation, and changing consumer behaviour could soon diminish the positive effects on prices, posing ongoing challenges for the sector. Economical changes over the past two decades have significantly restructured pig farming, highlighting a clear trend toward larger herds [109, 110]. Highly integrated operations with over a thousand sows continuously produce piglets on a weekly cycle, thereby creating a pig population with heterogeneous immunity [53, 111].

Older animals acquire immunity from previous infections and pass maternal antibodies to piglets. As previously mentioned, these antibodies initially protect piglets from disease symptoms but do not prevent infection, allowing even symptom-free piglets to carry and perpetuate virus circulation within the herd. This can lead to continuous virus circulation within the herd, with mutations allowing certain virus types to evade immune pressure and evolve into new variants, potentially resulting in the coexistence of multiple strains in the same population. Newborn piglets without prior exposure to the virus are particularly vulnerable, contributing to ongoing transmission. Around 5 to 8 weeks after birth, as maternal antibodies wane, piglets become susceptible to influenza once more. In large herds, the continuous presence of naive, unprotected age groups facilitates ongoing virus circulation, often leading to mild but persistent respiratory symptoms in weaned piglets and other age groups. Infections in suckling piglets are generally asymptomatic, but maternal immunity hinders the development of robust active immunity, leaving animals vulnerable to reinfection later [111, 112].

To effectively interrupt infection chains, thorough vaccination programs must be complemented by robust management of animal groups susceptible to the virus, including suckling piglets, weaned pigs, and young sows. A key factor is the strict separation of age groups, which helps target and break infection chains effectively [27, 49].
As the colder months approach in late autumn, these preventative measures become even more challenging [98]. Farmers may report that sows have fevers and decreased fertility

rates to their veterinarian [5, 49]. When responding to such reports, it is essential to consider other potential causes, such as a recent change in feed, as alterations in diet can also lead to similar symptoms [113].
Reducing non-infectious factors that contribute to respiratory illnesses is essential, as they are often straightforward to identify and can be systematically minimized, greatly lowering the risk of outbreaks. Additionally, maintaining strict biosecurity is critical; for instance, open doors between areas housing coughing piglets and sows can allow infections to spread to the sows [89]. Similarly, overlooking protocols, such as tending to younger piglets before older ones, can also elevate infection risks across groups [114].

Customized vaccination programs can help preventatively by reducing clinical symptoms, lowering lung viral loads, and minimizing viral shedding. Effective vaccines are available for both classical and pandemic strains of influenza. Currently, two approved vaccines for pigs exist in Germany. One for classical strain, H1N1, H1N2 and H3N2, and another for the pandemic H1pdmN1 strain [50, 99]. To achieve consistent herd immunity against swine influenza and improve welfare and production parameters, herd-specific vaccination strategies are recommended, particularly targeting sow immunization [109].
Respiporc Flu 3 is typically used for these herd vaccinations. Vaccination takes place when animals are initially housed, followed by a second dose three weeks later for primary immunization. Afterward, herd vaccination continues every 4 to 6 months, with a booster administered 14 days prior to farrowing to provide maternally derived immunity to piglets [101]. In contrast, Respiporc FLUpan H1N1 is usually implemented for active immunization in response to an ongoing outbreak [102].
Ideally, for effective integration management, unprotected gilts should be introduced with minimal integration dates, subjected to thorough quarantine protocols including testing for the influenza A virus and vaccinated before joining the main sow herd [90, 93].
In farms with a high outbreak risk, piglet or fattening pig vaccination is sometimes considered as an additional precautionary measure [62]. While the influenza vaccine does not provide "sterile immunity", meaning vaccinated animals can still carry viral material without showing clinical symptoms, the immunity conferred protects only those animals directly vaccinated. However, if vaccinations are stopped or not administered to piglets, there is a risk of recurring influenza infections [99].

Another aspect is natural exposure to swine influenza: the virus occurs year-round in various forms and often leads to a certain level of exposure in young animals. Many piglets survive the infection without severe symptoms, making early vaccination often unnecessary [115]. However, as mentioned earlier, this approach carries the risk that the virus remains latent within the herd and continues to circulate [111, 112].

Samples can be collected via nasal swabs or chewed cotton ropes, both of which can be prepared for PCR testing, with PCR proving most effective 24 to 72 hours after clinical symptoms first appear. Alternatively, blood samples preferably from unvaccinated animals can be tested for antibodies using ELISA. For accurate results, serum should be collected in two rounds, spaced 10 to 21 days apart, as antibodies generally become detectable 10 to 14 days post-infection [70]. To exclude other respiratory illnesses, additional pathogens, such as *Actinobacillus pleuropneumoniae*, *Haemophilus parasuis*, PCV-2 or PRRSV, may also be tested [116].

Diagnosing influenza is particularly challenging in cases of co-infection, requiring samples from different age groups. In cases where animals exhibit clear clinical symptoms, the influenza A virus may no longer be detectable by PCR. This is due to the virus being rapidly cleared from the body, which complicates accurate and timely diagnosis [117]. When the pandemic influenza virus is involved, the diagnosis becomes even more difficult and labour intensive [5]. Blood samples from sows vaccinated against classical strains are also hard to interpret due to cross-reactions between the vaccine and field strains [118].

In general, samples should be taken from age groups showing frequent signs of the disease. Sampling different age groups simultaneously provides the best overview of the influenza strains circulating in a herd [117]. Blood samples from rearing piglets are often unreliable for detecting influenza exposure, as maternal antibodies can suppress antibody development, leading to undetectable titers until the end of the rearing period. In contrast, paired serum samples from fattening pigs or young sows can yield good results [70].

A significant problem in swine influenza diagnostics is the diagnostic gap that arises between the acute phase, when PCR testing is effective, and the point when antibodies are detectable via ELISA. This diagnostic gap can pose challenges, which can be addressed through several strategies. Recommendations include meticulous sample collection from diverse animals at varying intervals, environmental swabbing to monitor infection spread, and combining PCR with ELISA testing to achieve a more comprehensive picture of the herd's infection status.

Together, these approaches improve diagnostic accuracy and provide a more comprehensive infection assessment [70, 119].

In the event of an influenza outbreak, only symptomatic treatment is possible, underscoring the importance of comprehensive preventative measures. When an influenza outbreak occurs, the primary focus shifts to symptom management. Influenza viruses, especially when compounded by co-infections, can lead to pneumonia and sudden death in pigs.
Supportive treatment involves ensuring proper hydration with water, along with the use of antipyretics, which are essential for reducing infection-related stress and lowering the risk of secondary infections [41]. Additionally, the herd veterinarian may consider antibiotic treatment, selected based on antibiogram results, to address bacterial secondary infections early on [81]. Once the animals have recovered and regained strength, vaccination can be administered [6].

Managing the challenges posed by swIAV on German pig farms requires a comprehensive approach focused on both prevention and early detection. The pandemic strain's persistence and vague clinical symptoms complicate diagnosis and control, making it crucial for farmers and veterinarians to implement targeted vaccination and health management programs. Proactive measures will be key to minimizing its impact on farm productivity and animal welfare.

10. Conclusion

In conclusion, the growing prevalence and persistent circulation of swIAV within German pig herds presents significant challenges for animal health and farm productivity [50, 107]. Unlike classical strains, which caused isolated outbreaks with distinct clinical signs, pandemic strains have transformed swIAV dynamics. The current swIAV strains circulate year-round, occurring in waves with often ambiguous symptoms and a subtle progression, leading to an endemic presence that is difficult to detect and control. The rise has led to more complex infection patterns that spread across multiple age groups, affecting reproduction, increasing antibiotic use, and weakening immune responses, which fosters secondary infections and limits herd immunity [34, 50, 53, 54].

The economic implications of swIAV in the pig farming industry are substantial, as the virus leads to increased costs in both treatment and production. The virus exacerbates respiratory issues, prolongs fattening periods, and impacts profitability by slowing growth rates, raising maintenance costs, and reducing feed efficiency [49, 50, 88].

In recent years, economic and structural changes in German pig farming, such as fewer but larger farms and rising production costs, have introduced new challenges in disease control [108, 110]. Larger, more heterogeneous herds with mixed-age groups create conditions favorable to continuous swIAV transmission, complicating infection management and raising the risk of persistent viral circulation. Together, these factors present ongoing challenges to maintaining both animal health and farm efficiency [111].

As a long-term strategy, proactive vaccination to help lower viral pressure, alongside measures to break infection chains, robust biosecurity, and early detection protocols, remain essential to safeguarding productivity and animal welfare while minimizing the financial losses associated with influenza outbreaks [27, 49, 89, 109].

A multifaceted approach is therefore essential. Vaccination programs must be carefully tailored, alongside biosecurity measures and management strategies, to reduce infection rates and improve animal welfare. Implementing preventive measures, such as strict separation of age groups and using vaccination, can curb virus transmission and mitigate swIAV's impact on farm productivity. For sustainable control, the collaboration of veterinarians and farmers, coupled with adaptive management, will be crucial to address these evolving challenges in the swine industry effectively [89, 109, 120].

11. Bibliography

1. Nelson MI, Viboud C, Vincent AL, Culhane MR, Detmer SE, Wentworth DE, Rambaut A, Suchard MA, Holmes EC, Lemey P (2015) Global migration of influenza A viruses in swine. Nat Commun 6:6696. https://doi.org/10.1038/ncomms7696
2. Neumann G, Kawaoka Y (2015) Transmission of influenza A viruses. Virology 479–480:234–246. https://doi.org/10.1016/j.virol.2015.03.009
3. Henritzi D, Petric PP, Lewis NS, Graaf A, Pessia A, Starick E, Breithaupt A, Strebelow G, Luttermann C, Parker LMK, Schröder C, Hammerschmidt B, Herrler G, Beilage EG, Stadlbauer D, Simon V, Krammer F, Wacheck S, Pesch S, Schwemmle M, Beer M, Harder TC (2020) Surveillance of European Domestic Pig Populations Identifies an Emerging Reservoir of Potentially Zoonotic Swine Influenza A Viruses. Cell Host & Microbe 28:614-627.e6. https://doi.org/10.1016/j.chom.2020.07.006
4. De Fougerolles TR, Baïssas T, Perquier G, Vitoux O, Crépey P, Bartelt-Hofer J, Bricout H, Petitjean A (2024) Public health and economic benefits of seasonal influenza vaccination in risk groups in France, Italy, Spain and the UK: state of play and perspectives. BMC Public Health 24:1222. https://doi.org/10.1186/s12889-024-18694-5
5. Ma W (2020) Swine influenza virus: Current status and challenge. Virus Research 288:198118. https://doi.org/10.1016/j.virusres.2020.198118
6. Sandbulte MR, Spickler AR, Zaabel PK, Roth JA (2015) Optimal Use of Vaccines for Control of Influenza A Virus in Swine. Vaccines (Basel) 3:22–73. https://doi.org/10.3390/vaccines3010022
7. Petro-Turnquist E, Pekarek MJ, Weaver EA (2024) Swine influenza A virus: challenges and novel vaccine strategies. Front Cell Infect Microbiol 14:1336013. https://doi.org/10.3389/fcimb.2024.1336013
8. Bouvier NM, Palese P (2008) The biology of influenza viruses. Vaccine 26:D49–D53. https://doi.org/10.1016/j.vaccine.2008.07.039
9. Kibenge FSB, Kibenge MJT (2016) Orthomyxoviruses of Fish. In: Aquaculture Virology. Elsevier, pp 299–326
10. Current ICTV Taxonomy Release | ICTV. https://ictv.global/taxonomy. Accessed 24 Mar 2024
11. D. Scott McVey, Melissa Kennedy, M. M. CHengappa, Rebecca Wilkes (2022) Veterinary Microbiology 4th Edition
12. Chen J, Deng Y-M (2009) Influenza virus antigenic variation, host antibody production and new approach to control epidemics. Virol J 6:30. https://doi.org/10.1186/1743-422X-6-30
13. Turrell L, Lyall JW, Tiley LS, Fodor E, Vreede FT (2013) The role and assembly mechanism of nucleoprotein in influenza A virus ribonucleoprotein complexes. Nat Commun 4:1591. https://doi.org/10.1038/ncomms2589
14. Mancera Gracia JC, Pearce DS, Masic A, Balasch M (2020) Influenza A Virus in Swine: Epidemiology, Challenges and Vaccination Strategies. Front Vet Sci 7:647. https://doi.org/10.3389/fvets.2020.00647
15. Kim H, Webster RG, Webby RJ (2018) Influenza Virus: Dealing with a Drifting and Shifting Pathogen. Viral Immunology 31:174–183. https://doi.org/10.1089/vim.2017.0141
16. Rabalski L, Kosinski M, Cybulski P, Stadejek T, Lepek K (2023) Genetic Diversity of Type A Influenza Viruses Found in Swine Herds in Northwestern Poland from 2017 to 2019: The One Health Perspective. Viruses 15:1893. https://doi.org/10.3390/v15091893

17. Chauhan RP, Gordon ML (2022) An overview of influenza A virus genes, protein functions, and replication cycle highlighting important updates. Virus Genes 58:255–269. https://doi.org/10.1007/s11262-022-01904-w
18. Boivin S, Cusack S, Ruigrok RWH, Hart DJ (2010) Influenza A Virus Polymerase: Structural Insights into Replication and Host Adaptation Mechanisms. Journal of Biological Chemistry 285:28411–28417. https://doi.org/10.1074/jbc.R110.117531
19. Taubenberger JK, Kash JC (2010) Influenza Virus Evolution, Host Adaptation, and Pandemic Formation. Cell Host & Microbe 7:440–451. https://doi.org/10.1016/j.chom.2010.05.009
20. Ma W, Lager KM, Lekcharoensuk P, Ulery ES, Janke BH, Solorzano A, Webby RJ, Garcia-Sastre A, Richt JA (2010) Viral reassortment and transmission after co-infection of pigs with classical H1N1 and triple-reassortant H3N2 swine influenza viruses. Journal of General Virology 91:2314–2321. https://doi.org/10.1099/vir.0.021402-0
21. McDonald SM, Nelson MI, Turner PE, Patton JT (2016) Reassortment in segmented RNA viruses: mechanisms and outcomes. Nat Rev Microbiol 14:448–460. https://doi.org/10.1038/nrmicro.2016.46
22. Lowen AC (2018) It's in the mix: Reassortment of segmented viral genomes. PLoS Pathog 14:e1007200. https://doi.org/10.1371/journal.ppat.1007200
23. Munster VJ, Baas C, Lexmond P, Waldenström J, Wallensten A, Fransson T, Rimmelzwaan GF, Beyer WEP, Schutten M, Olsen B, Osterhaus ADME, Fouchier RAM (2007) Spatial, temporal, and species variation in prevalence of influenza A viruses in wild migratory birds. PLoS Pathog 3:e61. https://doi.org/10.1371/journal.ppat.0030061
24. Short KR, Richard M, Verhagen JH, van Riel D, Schrauwen EJA, van den Brand JMA, Mänz B, Bodewes R, Herfst S (2015) One health, multiple challenges: The inter-species transmission of influenza A virus. One Health 1:1–13. https://doi.org/10.1016/j.onehlt.2015.03.001
25. Maclachlan NJ, Dubovi EJ, Barthold SW, Swayne DE, Winton JR (2017) Fenner's veterinary virology, Fifth edition. Elsevier/AP, Academic Press is an imprint of Elsevier, Amsterdam
26. Swine influenza. In: WOAH - World Organisation for Animal Health. https://www.woah.org/en/disease/swine-influenza/. Accessed 29 Mar 2024
27. Li Y, Robertson I (2021) The epidemiology of swine influenza. Anim Dis 1:21. https://doi.org/10.1186/s44149-021-00024-6
28. Reeth KV, Brown IH, Dürrwald R, Foni E, Labarque G, Lenihan P, Maldonado J, Markowska-Daniel I, Pensaert M, Pospisil Z, Koch G (2008) Seroprevalence of H1N1, H3N2 and H1N2 influenza viruses in pigs in seven European countries in 2002–2003. Influenza and Other Respiratory Viruses 2:99. https://doi.org/10.1111/j.1750-2659.2008.00043.x
29. Shope RE (1931) SWINE INFLUENZA : III. FILTRATION EXPERIMENTS AND ETIOLOGY. J Exp Med 54:373–385. https://doi.org/10.1084/jem.54.3.373
30. Cohen J (2010) Swine flu pandemic. What's old is new: 1918 virus matches 2009 H1N1 strain. Science 327:1563–1564. https://doi.org/10.1126/science.327.5973.1563
31. Watson SJ, Langat P, Reid SM, Lam TT-Y, Cotten M, Kelly M, Van Reeth K, Qiu Y, Simon G, Bonin E, Foni E, Chiapponi C, Larsen L, Hjulsager C, Markowska-Daniel I, Urbaniak K, Dürrwald R, Schlegel M, Huovilainen A, Davidson I, Dán Á, Loeffen W, Edwards S, Bublot M, Vila T, Maldonado J, Valls L, Brown IH, Pybus OG, Kellam P (2015) Molecular Epidemiology and Evolution of Influenza Viruses Circulating within European Swine between 2009 and 2013. J Virol 89:9920–9931. https://doi.org/10.1128/JVI.00840-15

32. Simon G, Larsen LE, Dürrwald R, Foni E, Harder T, Reeth KV, Markowska-Daniel I, Reid SM, Dan A, Maldonado J, Huovilainen A, Billinis C, Davidson I, Agüero M, Vila T, Hervé S, Breum SØ, Chiapponi C, Urbaniak K, Kyriakis CS, Consortium E, Brown IH, Loeffen W (2014) European Surveillance Network for Influenza in Pigs: Surveillance Programs, Diagnostic Tools and Swine Influenza Virus Subtypes Identified in 14 European Countries from 2010 to 2013. PLoS ONE 9:. https://doi.org/10.1371/journal.pone.0115815
33. Ma W, Gramer M, Rossow K, Yoon K-J (2006) Isolation and genetic characterization of new reassortant H3N1 swine influenza virus from pigs in the midwestern United States. J Virol 80:5092–5096. https://doi.org/10.1128/JVI.80.10.5092-5096.2006
34. Hennig C, Graaf A, Petric PP, Graf L, Schwemmle M, Beer M, Harder T (2022) Are pigs overestimated as a source of zoonotic influenza viruses? Porc Health Manag 8:30. https://doi.org/10.1186/s40813-022-00274-x
35. Starick E, Lange E, Grund C, grosse Beilage E, Döhring S, Maas A, Noé T, Beer M, Harder TC (2012) Reassortants of pandemic influenza A virus H1N1/2009 and endemic porcine HxN2 viruses emerge in swine populations in Germany. Journal of General Virology 93:1658–1663. https://doi.org/10.1099/vir.0.042648-0
36. Zell R, Groth M, Krumbholz A, Lange J, Philipps A, Dürrwald R (2020) Novel reassortant swine H3N2 influenza A viruses in Germany. Sci Rep 10:14296. https://doi.org/10.1038/s41598-020-71275-5
37. Harder TC, Grosse Beilage E, Lange E, Meiners C, Döhring S, Pesch S, Noé T, Grund C, Beer M, Starick E (2013) Expanded Cocirculation of Stable Subtypes, Emerging Lineages, and New Sporadic Reassortants of Porcine Influenza Viruses in Swine Populations in Northwest Germany. J Virol 87:10460–10476. https://doi.org/10.1128/JVI.00381-13
38. Long JS, Mistry B, Haslam SM, Barclay WS (2019) Host and viral determinants of influenza A virus species specificity. Nat Rev Microbiol 17:67–81. https://doi.org/10.1038/s41579-018-0115-z
39. Bourret V (2018) Avian influenza viruses in pigs: An overview. The Veterinary Journal 239:7–14. https://doi.org/10.1016/j.tvjl.2018.07.005
40. Janke BH (2014) Influenza A Virus Infections in Swine: Pathogenesis and Diagnosis. Vet Pathol 51:410–426. https://doi.org/10.1177/0300985813513043
41. WOAH (2009) Swine Influenza https://www.woah.org/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/SWINE_INFLUENZA.pdf
42. WOAH Terrestrial Manual (2023) Chapter 3.9.7. Influenza A viruses of swine https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/3.09.07_INF_A_SWINE.pdf
43. Abdelwhab EM, Mettenleiter TC (2023) Zoonotic Animal Influenza Virus and Potential Mixing Vessel Hosts. Viruses 15:980. https://doi.org/10.3390/v15040980
44. Kimble B, Nieto GR, Perez DR (2010) Characterization of influenza virus sialic acid receptors in minor poultry species. Virol J 7:365. https://doi.org/10.1186/1743-422X-7-365
45. Trebbien R, Larsen LE, Viuff BM (2011) Distribution of sialic acid receptors and influenza A virus of avian and swine origin in experimentally infected pigs. Virol J 8:434. https://doi.org/10.1186/1743-422X-8-434
46. Byrd-Leotis L, Liu R, Bradley KC, Lasanajak Y, Cummings SF, Song X, Heimburg-Molinaro J, Galloway SE, Culhane MR, Smith DF, Steinhauer DA, Cummings RD (2014) Shotgun glycomics of pig lung identifies natural endogenous receptors for

influenza viruses. Proc Natl Acad Sci USA 111:. https://doi.org/10.1073/pnas.1323162111
47. Nelli RK, Kuchipudi SV, White GA, Perez BB, Dunham SP, Chang K-C (2010) Comparative distribution of human and avian type sialic acid influenza receptors in the pig. BMC Vet Res 6:4. https://doi.org/10.1186/1746-6148-6-4
48. Mostafa A, Abdelwhab E, Mettenleiter T, Pleschka S (2018) Zoonotic Potential of Influenza A Viruses: A Comprehensive Overview. Viruses 10:497. https://doi.org/10.3390/v10090497
49. Gumbert S, Froehlich S, Rieger A, Stadler J, Ritzmann M, Zoels S (2020) Reproductive performance of pandemic influenza A virus infected sow herds before and after implementation of a vaccine against the influenza A (H1N1)pdm09 virus. Porc Health Manag 6:4. https://doi.org/10.1186/s40813-019-0141-x
50. Schmies K, Hennig C, Rose N, Fablet C, Harder T, grosse Beilage E, Graaf-Rau A (2024) Dynamic of swine influenza virus infection in weaned piglets in five enzootically infected herds in Germany, a cohort study. Porcine Health Management 10:36. https://doi.org/10.1186/s40813-024-00390-w
51. Vleeschauwer AD, Atanasova K, Borm SV, Berg T van den, Rasmussen TB, Uttenthal Å, Reeth KV (2009) Comparative Pathogenesis of an Avian H5N2 and a Swine H1N1 Influenza Virus in Pigs. PLOS ONE 4:e6662. https://doi.org/10.1371/journal.pone.0006662
52. Loeffen WLA, Kamp EM, Stockhofe-Zurwieden N, Van Nieuwstadt APKMI, Bongers JH, Hunneman WA, Elbers ARW, Baars J, Nell T, Van Zijderveld FG (1999) Survey of infectious agents involved in acute respiratory disease in finishing pigs. Veterinary Record 145:123–129. https://doi.org/10.1136/vr.145.5.123
53. Graaf-Rau A, Hennig C, Lillie-Jaschniski K, Koechling M, Stadler J, Boehmer J, Ripp U, Pohlmann A, Schwarz B-A, Beer M, Harder T (2023) Emergence of swine influenza A virus, porcine respirovirus 1 and swine orthopneumovirus in porcine respiratory disease in Germany. Emerging Microbes & Infections 12:2239938. https://doi.org/10.1080/22221751.2023.2239938
54. Rose N, Hervé S, Eveno E, Barbier N, Eono F, Dorenlor V, Andraud M, Camsusou C, Madec F, Simon G (2013) Dynamics of influenza A virus infections in permanently infected pig farms: evidence of recurrent infections, circulation of several swine influenza viruses and reassortment events. Veterinary Research 44:72. https://doi.org/10.1186/1297-9716-44-72
55. Sreta D, Tantawet S, Ayudhya SNN, Thontiravong A, Wongphatcharachai M, Lapkuntod J, Bunpapong N, Tuanudom R, Suradhat S, Vimolket L, Poovorawan Y, Thanawongnuwech R, Amonsin A, Kitikoon P (2010) Pandemic (H1N1) 2009 Virus on Commercial Swine Farm, Thailand. Emerging Infectious Diseases 16:1587. https://doi.org/10.3201/eid1610.100665
56. Diseases of the Respiratory System (2017). Veterinary Medicine 845–1090. https://doi.org/10.1016/B978-0-7020-5246-0.00012-7
57. Maes D, Peltoniemi O, Malik M (2023) Abortion and fetal death in sows. Reprod Domest Anim 58 Suppl 2:125–136. https://doi.org/10.1111/rda.14436
58. Hemmink JD, Morgan SB, Aramouni M, Everett H, Salguero FJ, Canini L, Porter E, Chase-Topping M, Beck K, Loughlin RM, Carr BV, Brown IH, Bailey M, Woolhouse M, Brookes SM, Charleston B, Tchilian E (2016) Distinct immune responses and virus shedding in pigs following aerosol, intra-nasal and contact infection with pandemic swine influenza A virus, A(H1N1)09. Vet Res 47:103. https://doi.org/10.1186/s13567-016-0390-5

59. Papatsiros VG, Papakonstantinou GI, Meletis E, Koutoulis K, Athanasakopoulou Z, Maragkakis G, Labronikou G, Terzidis I, Kostoulas P, Billinis C (2023) Seroprevalence of Swine Influenza A Virus (swIAV) Infections in Commercial Farrow-to-Finish Pig Farms in Greece. Vet Sci 10:599. https://doi.org/10.3390/vetsci10100599
60. Van Reeth K, Pensaert M (1994) Prevalence of infections with enzootic respiratory and enteric viruses in feeder pigs entering fattening herds. The Vet Rec 135:594-597. PMID: 7900243
61. Thacker EL, Thacker BJ, Janke BH (2001) Interaction between *Mycoplasma hyopneumoniae* and Swine Influenza Virus. J Clin Microbiol 39:2525–2530. https://doi.org/10.1128/JCM.39.7.2525-2530.2001
62. Salvesen HA, Whitelaw CBA (2021) Current and prospective control strategies of influenza A virus in swine. Porc Health Manag 7:23. https://doi.org/10.1186/s40813-021-00196-0
63. Mooij P, Koopman G, Mortier D, Van Heteren M, Oostermeijer H, Fagrouch Z, De Laat R, Kobinger G, Li Y, Remarque EJ, Kondova I, Verschoor EJ, Bogers WMJM (2015) Pandemic Swine-Origin H1N1 Influenza Virus Replicates to Higher Levels and Induces More Fever and Acute Inflammatory Cytokines in Cynomolgus versus Rhesus Monkeys and Can Replicate in Common Marmosets. PLoS ONE 10:e0126132. https://doi.org/10.1371/journal.pone.0126132
64. Richt JA, Lager KM, Janke BH, Woods RD, Webster RG, Webby RJ (2003) Pathogenic and Antigenic Properties of Phylogenetically Distinct Reassortant H3N2 Swine Influenza Viruses Cocirculating in the United States. J Clin Microbiol 41:3198–3205. https://doi.org/10.1128/JCM.41.7.3198-3205.2003
65. Gauger PC, Vincent AL, Loving CL, Henningson JN, Lager KM, Janke BH, Kehrli ME, Roth JA (2012) Kinetics of Lung Lesion Development and Pro-Inflammatory Cytokine Response in Pigs With Vaccine-Associated Enhanced Respiratory Disease Induced by Challenge With Pandemic (2009) A/H1N1 Influenza Virus. Vet Pathol 49:900–912. https://doi.org/10.1177/0300985812439724
66. Mukhopadhyay S, Philip AT, Stoppacher R (2010) Pathologic Findings in Novel Influenza A (H1N1) Virus ("Swine Flu") Infection: Contrasting Clinical Manifestations and Lung Pathology in Two Fatal Cases. American Journal of Clinical Pathology 133:380–387. https://doi.org/10.1309/AJCPXY17SULQKSWK
67. Richt JA, Webby RJ (2013) Swine Influenza. Springer Berlin Heidelberg, Berlin, Heidelberg
68. Saade G, Deblanc C, Bougon J, Marois-Créhan C, Fablet C, Auray G, Belloc C, Leblanc-Maridor M, Gagnon CA, Zhu J, Gottschalk M, Summerfield A, Simon G, Bertho N, Meurens F (2020) Coinfections and their molecular consequences in the porcine respiratory tract. Veterinary Research 51:80. https://doi.org/10.1186/s13567-020-00807-8
69. Landolt GA, Karasin AI, Phillips L, Olsen CW (2003) Comparison of the Pathogenesis of Two Genetically Different H3N2 Influenza A Viruses in Pigs. Journal of Clinical Microbiology 41:1936–1941. https://doi.org/10.1128/jcm.41.5.1936-1941.2003
70. Muzykina L, Barrado-Gil L, Gonzalez-Bulnes A, Crespo-Piazuelo D, Cerón JJ, Alonso C, Montoya M (2024) Overview of Modern Commercial Kits for Laboratory Diagnosis of African Swine Fever and Swine Influenza A Viruses. Viruses 16:505. https://doi.org/10.3390/v16040505
71. Cunha BA (2010) Swine Influenza (H1N1) Pneumonia: Clinical Considerations. Infect Dis Clin North Am 24:203–228. https://doi.org/10.1016/j.idc.2009.10.001
72. Decorte I, Steensels M, Lambrecht B, Cay AB, De Regge N (2015) Detection and Isolation of Swine Influenza A Virus in Spiked Oral Fluid and Samples from

Individually Housed, Experimentally Infected Pigs: Potential Role of Porcine Oral Fluid in Active Influenza A Virus Surveillance in Swine. PLoS One 10:e0139586. https://doi.org/10.1371/journal.pone.0139586
73. Grau K, Lillie-Jaschniski K, Graaf-Rau A, Harder T, Eddicks M, Zöls S, Zablotski Y, Ritzmann M, Stadler J (2024) Effect of stabilizers on the detection of swine influenza A virus (swIAV) in spiked oral fluids over time https://doi.org/10.21203/rs.3.rs-4486513/v1
74. Stadler J, Zwickl S, Gumbert S, Ritzmann M, Lillie-Jaschniski K, Harder T, Graaf-Rau A, Skampardonis V, Eddicks M (2024) Influenza surveillance in pigs: balancing act between broad diagnostic coverage and specific virus characterization. Porc Health Manag 10:19. https://doi.org/10.1186/s40813-024-00367-9
75. Detmer S, Gramer M, Goyal S, Torremorell M, Torrison J (2012) Diagnostics and Surveillance for Swine Influenza. In: Richt JA, Webby RJ (eds) Swine Influenza. Springer Berlin Heidelberg, Berlin, Heidelberg, pp 85–112
76. Goodell CK, Prickett J, Kittawornrat A, Johnson J, Zhang J, Wang C, Zimmerman JJ (2016) Evaluation of Screening Assays for the Detection of Influenza A Virus Serum Antibodies in Swine. Transbound Emerg Dis 63:24–35. https://doi.org/10.1111/tbed.12214
77. Deblanc C, Quéguiner S, Gorin S, Richard G, Moro A, Barbier N, Le Diguerher G, Paboeuf F, Hervé S, Simon G (2024) Pathogenicity and escape to pre-existing immunity of a new genotype of swine influenza H1N2 virus that emerged in France in 2020. Veterinary Research 55:65. https://doi.org/10.1186/s13567-024-01319-5
78. Andraud M, Hervé S, Gorin S, Barbier N, Quéguiner S, Paboeuf F, Simon G, Rose N (2023) Evaluation of early single dose vaccination on swine influenza A virus transmission in piglets: From experimental data to mechanistic modelling. Vaccine 41:3119–3127. https://doi.org/10.1016/j.vaccine.2023.04.018
79. Allerson M, Deen J, Detmer SE, Gramer MR, Joo HS, Romagosa A, Torremorell M (2013) The impact of maternally derived immunity on influenza A virus transmission in neonatal pig populations. Vaccine 31:500–505. https://doi.org/10.1016/j.vaccine.2012.11.023
80. Mughini-Gras L, Beato MS, Angeloni G, Monne I, Buniolo F, Zuliani F, Morini M, Castellan A, Bonfanti L, Marangon S (2015) Control of a Reassortant Pandemic 2009 H1N1 Influenza Virus Outbreak in an Intensive Swine Breeding Farm: Effect of Vaccination and Enhanced Farm Management Practices. PLoS Curr 7:ecurrents.outbreaks.4211b8d6cedd8c870db723455409c0f8. https://doi.org/10.1371/currents.outbreaks.4211b8d6cedd8c870db723455409c0f8
81. Helke KL, Ezell PC, Duran-Struuck R, Swindle MM (2015) Biology and Diseases of Swine. Laboratory Animal Medicine 695. https://doi.org/10.1016/B978-0-12-409527-4.00016-X
82. Schoos A, Devreese M, Maes DG (2019) Use of non-steroidal anti-inflammatory drugs in porcine health management. Veterinary Record 185:172–172. https://doi.org/10.1136/vr.105170
83. Lopez-Moreno G, Schmitt C, Spronk T, Culhane M, Torremorell M (2022) Evaluation of internal farm biosecurity measures combined with sow vaccination to prevent influenza A virus infection in groups of due-to-wean pigs. BMC Vet Res 18:393. https://doi.org/10.1186/s12917-022-03494-z
84. Mastin A, Alarcon P, Pfeiffer D, Wood J, Williamson S, Brown I, Wieland B (2011) Prevalence and risk factors for swine influenza virus infection in the English pig population. PLoS Curr 3:RRN1209. https://doi.org/10.1371/currents.RRN1209

85. Gonzalez-Reiche AS, Ramírez AL, Müller ML, Orellana D, Sosa SM, Ola P, Paniagua J, Ortíz L, Hernandez J, Cordón-Rosales C, Perez DR (2017) Origin, distribution, and potential risk factors associated with influenza A virus in swine in two production systems in Guatemala. Influenza Other Respir Viruses 11:182–192. https://doi.org/10.1111/irv.12437
86. Takemae N, Harada M, Nguyen PT, Nguyen T, Nguyen TN, To TL, Nguyen TD, Pham VP, Le VT, Do HT, Vo HV, Le QVT, Tran TM, Nguyen TD, Thai PD, Nguyen DH, Le AQT, Nguyen DT, Uchida Y, Saito T (2016) Influenza A Viruses of Swine (IAV-S) in Vietnam from 2010 to 2015: Multiple Introductions of A(H1N1)pdm09 Viruses into the Pig Population and Diversifying Genetic Constellations of Enzootic IAV-S. J Virol 91:e01490-16. https://doi.org/10.1128/JVI.01490-16
87. Li Y, Edwards J, Wang Y, Zhang G, Cai C, Zhao M, Huang B, Robertson ID (2019) Prevalence, distribution and risk factors of farmer reported swine influenza infection in Guangdong Province, China. Prev Vet Med 167:1–8. https://doi.org/10.1016/j.prevetmed.2019.03.011
88. Fablet C, Simon G, Dorenlor V, Eono F, Eveno E, Gorin S, Quéguiner S, Madec F, Rose N (2013) Different herd level factors associated with H1N1 or H1N2 influenza virus infections in fattening pigs. Prev Vet Med 112:257–265. https://doi.org/10.1016/j.prevetmed.2013.07.006
89. Ciuoderis-Aponte K, Diaz A, Muskus C, Peña M, Hernández-Ortiz J, Osorio J (2022) Farm management practices, biosecurity and influenza a virus detection in swine farms: a comprehensive study in Colombia. Porc Health Manag 8:42. https://doi.org/10.1186/s40813-022-00287-6
90. Simon-Grifé M, Martín-Valls GE, Vilar MJ, García-Bocanegra I, Mora M, Martín M, Mateu E, Casal J (2011) Seroprevalence and risk factors of swine influenza in Spain. Veterinary Microbiology 149:56–63. https://doi.org/10.1016/j.vetmic.2010.10.015
91. Baudon E, Peyre M, Peiris M, Cowling BJ (2017) Epidemiological features of influenza circulation in swine populations: A systematic review and meta-analysis. PLOS ONE 12:e0179044. https://doi.org/10.1371/journal.pone.0179044
92. Dupont K, Hjulsager CK, Kristensen CS, Baekbo P, Larsen LE (2009) Transmission of different variants of PCV2 and viral dynamics in a research facility with pigs mingled from PMWS-affected herds and non-affected herds. Vet Microbiol 139:219–226. https://doi.org/10.1016/j.vetmic.2009.06.001
93. Serafini Poeta Silva AP, De Freitas Costa E, Sousa E Silva G, Souza CK, Schaefer R, Da Silva Vaz I, Corbellini LG (2019) Biosecurity practices associated with influenza A virus seroprevalence in sows from southern Brazilian breeding herds. Preventive Veterinary Medicine 166:1–7. https://doi.org/10.1016/j.prevetmed.2019.02.013
94. Grøntvedt CA, Er C, Gjerset B, Hauge AG, Brun E, Jørgensen A, Lium B, Framstad T (2013) Influenza A(H1N1)pdm09 virus infection in Norwegian swine herds 2009/10: The risk of human to swine transmission. Prev Vet Med 110:429–434. https://doi.org/10.1016/j.prevetmed.2013.02.016
95. Schmies K, Harder T, Graaf A, Beilage E große (2023) Influenzavirus-Infektionen bei Schweinen: Risikofaktoren und Risikominimierung. Der Praktische Tierarzt 104:
96. Yan Z-L, Liu W-H, Long Y-X, Ming B-W, Yang Z, Qin P-Z, Ou C-Q, Li L (2024) Effects of meteorological factors on influenza transmissibility by virus type/subtype. BMC Public Health 24:494. https://doi.org/10.1186/s12889-024-17961-9
97. (2024) A systematic review of influenza virus in water environments across human, poultry, and wild bird habitats. Water Research X 22:100210. https://doi.org/10.1016/j.wroa.2023.100210

98. Chantziaras I, De Meyer D, Vrielinck L, Van Limbergen T, Pineiro C, Dewulf J, Kyriazakis I, Maes D (2020) Environment-, health-, performance- and welfare-related parameters in pig barns with natural and mechanical ventilation. Preventive Veterinary Medicine 183:105150. https://doi.org/10.1016/j.prevetmed.2020.105150
99. Graaf-Rau A, Schmies K, Breithaupt A, Ciminski K, Zimmer G, Summerfield A, Sehl-Ewert J, Lillie-Jaschniski K, Helmer C, Bielenberg W, Grosse Beilage E, Schwemmle M, Beer M, Harder T (2024) Reassortment incompetent live attenuated and replicon influenza vaccines provide improved protection against influenza in piglets. npj Vaccines 9:127. https://doi.org/10.1038/s41541-024-00916-x
100. Li C, Culhane MR, Schroeder DC, Cheeran MC-J, Galina Pantoja L, Jansen ML, Torremorell M Vaccination decreases the risk of influenza A virus reassortment but not genetic variation in pigs. eLife 11:e78618. https://doi.org/10.7554/eLife.78618
101. Ceva Santé Animale. Marketing Authorisation Details for Respiporc Flu 3. European Medicines Agency, 2010. EU/2/09/103/001-007.
102. Ceva Santé Animale. Marketing Authorisation Details for Respiporc Flupan H1N1. European Medicines Agency, 2017. EU/2/17/209/001-002.
103. Vincent AL, Perez DR, Rajao D, Anderson TK, Abente EJ, Walia RR, Lewis NS (2017) Influenza A virus vaccines for swine. Vet Microbiol 206:35–44. https://doi.org/10.1016/j.vetmic.2016.11.026
104. Larsen DL, Karasin A, Zuckermann F, Olsen CW (2000) Systemic and mucosal immune responses to H1N1 influenza virus infection in pigs. Vet Microbiol 74:117–131. https://doi.org/10.1016/s0378-1135(00)00172-3
105. Markowska-Daniel I, Urbaniak K, Porowski M, Karbowiak P, Kowalczyk A, Kozak E, Pejsak Z (2013) Emergence of the pandemic H1N1 2009 influenza A virus in swine herds in Poland. Bulletin of the Veterinary Institute in Pulawy 57:293–300. https://doi.org/10.2478/bvip-2013-0051
106. Kwit K, Pomorska-Mól M, Markowska-Daniel I (2015) Pregnancy outcome and clinical status of gilts following experimental infection by H1N2, H3N2 and H1N1pdm09 influenza A viruses during the last month of gestation. Arch Virol 160:2415–2425. https://doi.org/10.1007/s00705-015-2518-8
107. Dynamic Flu Map. In: Swine Ceva. https://swine.ceva.com/home/diseases/swine-influenza/dynamic-swine-flu-map/. Accessed 12 Nov 2024
108. Zahl der schweinehaltenden Betriebe geht weiter zurück. In: Statistisches Bundesamt. https://www.destatis.de/DE/Themen/Branchen-Unternehmen/Landwirtschaft-Forstwirtschaft-Fischerei/Tiere-Tierische-Erzeugung/schweine.html. Accessed 6 Nov 2024
109. Maes DGD, Dewulf J, Piñeiro C, Edwards S, Kyriazakis I (2020) A critical reflection on intensive pork production with an emphasis on animal health and welfare. Journal of Animal Science 98:S15. https://doi.org/10.1093/jas/skz362
110. Thiermann I, Schröer D, Latacz-Lohmann U (2023) Are German farmers ready for a ‘warm restructuring’ of the pig sector? Ecological Economics 209:107853. https://doi.org/10.1016/j.ecolecon.2023.107853
111. Cador C, Hervé S, Andraud M, Gorin S, Paboeuf F, Barbier N, Quéguiner S, Deblanc C, Simon G, Rose N (2016) Maternally-derived antibodies do not prevent transmission of swine influenza A virus between pigs. Veterinary Research 47:86. https://doi.org/10.1186/s13567-016-0365-6
112. Ryt-Hansen P, Pedersen AG, Larsen I, Krog JS, Kristensen CS, Larsen LE (2019) Acute Influenza A virus outbreak in an enzootic infected sow herd: Impact on viral dynamics, genetic and antigenic variability and effect of maternally derived antibodies

and vaccination. PLoS ONE 14:e0224854. https://doi.org/10.1371/journal.pone.0224854
113. Peltoniemi OA, Oliviero C, Hälli O, Heinonen M (2007) Feeding affects reproductive performance and reproductive endocrinology in the gilt and sow. Acta Vet Scand 49:S6. https://doi.org/10.1186/1751-0147-49-S1-S6
114. Bernaerdt E, Díaz I, Piñeiro C, Collell M, Dewulf J, Maes D (2023) Optimizing internal biosecurity on pig farms by assessing movements of farm staff. Porcine Health Management 9:11. https://doi.org/10.1186/s40813-023-00310-4
115. Ryt-Hansen P, Larsen I, Kristensen CS, Krog JS, Wacheck S, Larsen LE (2019) Longitudinal field studies reveal early infection and persistence of influenza A virus in piglets despite the presence of maternally derived antibodies. Veterinary Research 50:36. https://doi.org/10.1186/s13567-019-0655-x
116. Sarli G, D'Annunzio G, Gobbo F, Benazzi C, Ostanello F (2021) The Role of Pathology in the Diagnosis of Swine Respiratory Disease. Veterinary Sciences 8:256. https://doi.org/10.3390/vetsci8110256
117. Lillie-Jaschniski K, Lisgara M, Pileri E, Jardin A, Velazquez E, Köchling M, Albin M, Casanovas C, Skampardonis V, Stadler J (2022) A New Sampling Approach for the Detection of Swine Influenza a Virus on European Sow Farms. Veterinary Sciences 9:338. https://doi.org/10.3390/vetsci9070338
118. Kitikoon P, Gauger PC, Anderson TK, Culhane MR, Swenson S, Loving CL, Perez DR, Vincent AL (2013) Swine influenza virus vaccine serologic cross-reactivity to contemporary US swine H3N2 and efficacy in pigs infected with an H3N2 similar to 2011–2012 H3N2v. Influenza and Other Respiratory Viruses 7:32. https://doi.org/10.1111/irv.12189
119. Garrido-Mantilla J, Alvarez J, Culhane M, Nirmala J, Cano JP, Torremorell M (2019) Comparison of individual, group and environmental sampling strategies to conduct influenza surveillance in pigs. BMC Vet Res 15:61. https://doi.org/10.1186/s12917-019-1805-0
120. White LA, Torremorell M, Craft ME (2017) Influenza A virus in swine breeding herds: Combination of vaccination and biosecurity practices can reduce likelihood of endemic piglet reservoir. Preventive Veterinary Medicine 138:55–69. https://doi.org/10.1016/j.prevetmed.2016.12.013

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