

# Equine influenza in Brazil

## *A influenza equina no Brasil*

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### Abstract

Equine influenza virus (EIV) (H3N8 and H7N7) is the causative agent of equine influenza, or equine flu. The H7N7 subtype has been considered to be extinct worldwide since 1980. Affected animals have respiratory symptoms that can be worsened by secondary bacterial respiratory infection, thereby leading to great economic losses in the horse-breeding industry. In Brazil, equine influenza outbreaks were first reported in 1963 and studies on hemagglutination antibodies against viral subtypes in Brazilian horses have been conducted since then. The objective of the present review was to present the history of the emergence of EIV around the world and in Brazil and the studies that have thus far been developed on EIV in Brazilian equines.

**Keywords:** Equine influenza virus. Equines. Brazil.

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### Resumo

O vírus da influenza equina (EIV) (H3N8 e H7N7) é o agente causador da influenza equina, ou gripe equina. O subtipo viral H7N7 é considerado como mundialmente extinto desde 1980. Os animais afetados têm sintomas respiratórios característicos que podem ser agravados por uma infecção respiratória bacteriana secundária causando grandes prejuízos no ramo equestre. No Brasil, os surtos da EI têm sido relatados desde 1963 e desde então vem sendo efetuados estudos sobre a presença de anticorpos hemaglutinantes contra os subtipos virais nos equídeos brasileiros. O presente artigo tem o objetivo de apresentar um histórico sobre o surgimento do EIV no mundo e no Brasil destacando os estudos conduzidos no Brasil até o momento acerca da infecção pelo EIV nos equídeos brasileiros.

**Palavras-chave:** Vírus da influenza equina. Equídeos. Brasil.

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### Introduction

The horse-breeding business is an important economic segment in Brazil. Its estimated annual turnover is approximately R\$ 7.3 billion and it is

responsible for around 3.2 million direct and indirect jobs (BRAZIL, 2013).

According to IBGE (2014), Brazil has a horse population of approximately 5.32 million. São Paulo is the fifth largest state, with 347,411 horses, which represent 6.54% of the Brazilian horse population (IBGE, 2014) (Table 1). The combined total number of horses, donkeys and mules in Brazil has been estimated at million animals (BRAZIL, 2013).

In order to promote surveillance and control over equine diseases of sanitary importance, the National Program for Equine Health (PNSE) was established by the Ministry of Agriculture, Livestock and Food Supply (MAPA) through Normative Instruction no. 17, in May 2008 (BRAZIL, 2008).

Table 1 – Equine population in five Brazilian states with largest numbers of horses in the country – 2014

Brazilian state	No. of horses	%	Ranking
Minas Gerais	758,880	14.28	1
Rio Grande do Sul	535,299	10.07	2
Bahia	485,356	9.13	3
Goiás	394,799	7.43	4
Sao Paulo	347,411	6.54	5

Source: IBGE (2014)

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Movement of horses within Brazil is subject to presentation of an animal movement permit (GTA), which is issued only if the animal has tested negative for equine infectious anemia. If the horse is in a Brazilian state where cases of glanders have been confirmed, the animal needs to be negative for this as well (BRAZIL, 2009).

In cases of interstate transportation or equestrian events, a certificate for equine influenza (EI) vaccination and/or a certificate for non-occurrence of EI over a 30-day period prior to issuing the animal movement permit is required (DDA no. 17, Nov. 2001) (BRAZIL, 2001).

Since influenza is related to human disease, the term *equine influenza* was likewise correlated with acute respiratory diseases in horses (WADDELL et al., 1963).

Subsequent to isolation and identification of equine influenza virus (EIV), the term *equine influenza* was applied generically to respiratory and systemic diseases, called *influenza-abortion disorders*. In 1957, however, *influenza-abortion disorders* were found to be caused by another filterable virus and not by EIV (DOLL et al., 1957).

An outbreak occurred in Sweden in 1955, in which horses had symptoms in the upper respiratory tract. Through seroconversion in the hemagglutination-

inhibition (HI) test, it was suggested that this outbreak had been caused by influenza A virus (HELLER et al., 1956).

In 1956, EIV was first isolated from horses with respiratory symptoms in Czechoslovakia (A/equine/Prague/1/56 - H7N7) (SONIVOVA et al., 1958).

In February 1963, a highly contagious acute respiratory disease suddenly occurred in horses and ponies in Florida. The clinical signs were consistent with and similar to those of diseases that are generically called influenza (DOLL, 1963). The animals presented fever, coughing and nasal discharge, with congestion of mucous membranes in some animals, muscle tremors in cases of severe fever and lack of appetite early in the disease course. New cases continued to occur in that region until April 1963, and it was estimated that between 60 and 70% of all the adult animals had the disease (WADDELL et al., 1963).

The 1963 Florida outbreak was associated with a distinct virus that had previously been correlated with respiratory disease in horses (H7N7 - A/equine/Prague/1/56). This was the first report of isolation and identification of an equine H3N8 subtype called A/equine/Miami/1/1963 (H3N8). This resulted from a major antigenic shift in which EIV with hemagglutinin (HA) and neuraminidase (NA) underwent significant changes (WADDELL et al., 1963).

Both subtypes (H3N8 and H7N7) often cause similar symptoms, such as coughing, fever, lack of appetite, muscle pain, secondary pneumonia and tracheobronchitis, but subtype H3N8 often produces

greater disease severity (BEVERIDGE, 1965), including occurrence of interstitial myocarditis (GERBER, 1969).

Reports on occurrences of respiratory disease epidemics in horses and humans in Europe in the pre-virological era that were believed to be due to influenza infection date back to the time of discovery of influenza viruses in animals and humans (MORENS, TAUBENBERGER, 2010).

Although there are few reports of human infection with EIV, there is a zoonotic risk and possibility of interspecies infection (KASEL; COUCH, 1969; BERRÍOS, 2005; CRAWFORD et al., 2005).

Experimental infection with the H3N8 equine virus (A/equine/Miami/1963) in human volunteers in 1969 resulted in fever and affected the upper respiratory tract and/or lower respiratory tract (KASEL; COUCH, 1969).

Recently, the H3N8 equine virus was found to have broken through the inter-host barrier, thus causing infections in dogs (CRAWFORD et al., 2005) and pigs (TU et al., 2009).

The outbreak of H3N8 in dogs was characterized by severe respiratory disease and the virus was closely related to the H3N8 equine influenza virus (CRAWFORD et al., 2005).

The first report of the EIV H3N8 subtype in Brazil was in 1963, in the state of São Paulo, and was named A/equi/SP/63 (ANDREWS et al., 1978).

In July 1976, a H7N7 subtype was isolated from nasal discharge from horses in the state of São Paulo (A/equi/SP/1/76) during an outbreak of respiratory disease. Paired horse sera showed higher HI titers against A/equi/SP/1/76 than against A/equine/Prague/1/56 (PIEGAS et al., 1976).

In 1969, outbreaks occurred in São Paulo-SP (PEREIRA et al., 1972) and Guanabara-RJ (CUNHA et al., 1970) in equestrian establishments (SP and RJ) and in the cavalry of the military police of São Paulo, both related to the H3N8 subtype.

Paired serum samples were collected from animals affected by the 1969 outbreak (São Paulo) and were HI-tested against H7N7 (A/equine/Prague/1/56) and H3N8 (A/equine/Miami/63 and A/equine/SP/6/69). The animals showed highest serum conversion to São Paulo/6/69, followed by Miami/63, while few animals showed serum conversion to Prague/1/56 (PEREIRA et al., 1972). The São Paulo/6/69 and Miami/63 strains also reacted in the HI test against hyperimmune sera from ferrets (inoculated with the three viral variants) and showed antigenic differences in HI cross-reactions. Therefore, it was suggested that the observed antigenic variation occurred at different sites responsible for HI cross-reactions, as had previously been reported by Tumová and Pereira (1968) using Miami/63 and human H3N2 (A/HK/68) (PEREIRA et al., 1972).

In 1976, there were EI outbreaks caused by the H7N7 subtype in the states of São Paulo (PIEGAS et al., 1976) and Rio de Janeiro (CUNHA et al., 1978). Animals affected in Rio de Janeiro had the usual EI clinical signs, which spread to all animals on the same farm within one week, although with a benign course and no mortality (CUNHA et al., 1978).

In July 1985, an outbreak of equine influenza occurred in the city of Rio de Janeiro, affecting two large equestrian clubs in the city. The animals presented fever, coughing and nose discharge, with a short benign course and without secondary complications (CUNHA et al., 1986).

The virus isolated from the 1985 outbreak in Rio de Janeiro (RJ/85) was classified using hyperimmune sera that were prepared from the newly isolated virus (RJ/85), two previous Brazilian virus, H3N8 (A/equi/GB/69) and H7N7 (A/Equi/RJ/76), and a hyperimmune serum standard, H3N8 (A/equine/Miami/63), from CDC-Atlanta. The immune sera RJ/85, GB/69 and Miami/63 inhibited the newly isolated virus and GB/69 but did not inhibit the H7N7 virus, thus suggesting that RJ/85 was the subtype H3N8 (CUNHA et al., 1986). In 2001, the H3N8

subtype was again identified in the state of Rio de Janeiro (LOUREIRO, 2004).

In 1988, Mancini et al. described an outbreak caused by the H3N8 subtype on a farm in São Roque-SP. Serum samples were obtained from 95 animals at 40 and 80 days after onset of the disease. HI tests against H7N7 (A/equi/SP/1/56) and H3N8 (A/equi/SP/1/85) and single radial hemolysis were performed. The serum panel had higher identity with H3N8 (HI  $\geq$  40 and HPS  $\geq$  4.5

serum sample was positive for H7N7, thus suggesting that a H3N8 subtype caused the outbreak (MANCINI et al., 1988).

According to the World Organization for Animal Health (OIE), the EIV outbreaks that occurred in Brazil in 2008 and 2010 were caused by the H3N8 subtype. Viruses were isolated but the viral strains were not described (OIE, 2009a; OIE, 2011a). EIV outbreaks in Brazil were also reported in 2009 and from 2011 to 2014 (Table 2) and only one

Table 2 – Brazilian reports to the OIE notifying the presence of equine influenza in the years 2008-2014

Year	Outbreaks	Cases	Deaths	Routinely vaccinated
2008	45	272	-	18354
2009	59	185	-	25183
2010	3	3	-	17053
2011	24	62	-	15503
2012	29	1382	2	23494
2013	4	12	-	9114
2014	4	7	-	7084

Source: OIE (2009b, 2010, 2011b, 2012, 2013b, 2015)

According to the OIE, the equine H3N8 subtype was isolated and/or characterized from many outbreaks in 2012: in Argentina, Chile, France, Germany, Ireland, United Kingdom, Uruguay and United States (OIE, 2013a); and in Brazil, thereby causing deaths in France, Brazil and Uruguay (OIE, 2013b). EIV (H3N8) was isolated and/or characterized in quarantine stations from horses recently imported from Uruguay to Dubai and from Belgium to Japan. The outbreaks occurred in horses both with and without vaccination. Approximately 150 vaccinated horses were affected in three linked outbreaks in the Calvados area in France. All the viruses identified in the 2012 outbreaks belong to the Florida cluster, clades 1 and 2 (OIE, 2013a).

One EIV (H3N8) strain was isolated from the Brazilian outbreak in 2012 and was named A/equine/Sao Paulo/IB19/2012 (GenBank accession number KC620391.1) (VILLALOBOS et al., 2013). HA and NA sequences were obtained from one sample

(A/equine/Sao Paulo/1.19/2012) from the Brazilian outbreak of 2012 and this showed that the strain belonged to Florida clade 1 (VILLALOBOS et al., 2013; FILIPPSEN et al., 2015). In the same year, Brazil had 29 outbreaks comprising 1382 cases and two deaths, which were reported to the OIE (OIE, 2013b).

Aguiar et al., in a study on the seroprevalence of EIV (H7N7 and H3N8), in which the aim was to detect hemagglutination-inhibiting antibodies in horses in Monte Negro, state of Rondônia, in the western Brazilian Amazon region, analyzed serum samples from 176 horses and mules. They found that the prevalence of H7N7 was 19.9% and of H3N8, 42%. The latter was statistically greater (AGUIAR et al., 2008).

Positive HI results of between 30 and 65% were obtained in previous studies in Rio Grande do Sul (DIEL et al., 2006), Pantanal (SILVA et al., 1999), Rio de Janeiro (OLIVEIRA et al., 2005) and Pará (HEINEMANN et al., 2009).

Analysis of previous serological surveys on populations of asymptomatic equines in several

locations in Brazil suggests that infection with EIV is in an endemic situation (Table 3).

Table 3 – Serological surveys for inhibitory antibodies for EIV hemagglutinin in equines in Brazil – 2015

N	Authors	Serum treatment to remove nonspecific inhibitors of hemagglutination	Subtype	Antibodies investigated through HI assay (%)	Number of animals	State	Type	Vaccination
1	Pagano et al. 1985	He/P/D	H7N7 <sup>f</sup>	77.75	1344	AP, PA, RR, AM, AC and RO	CS	nv
			H3N8 <sup>g</sup>	41.22				
			H7N7 <sup>f</sup>	30.64	718	CE, PB and PE	CS	nv
			H3N8 <sup>g</sup>	24.79				
			H7N7	61.72	1343	RJ	CS	nd
			H3N8 <sup>g</sup>	42.06				
			H7N7 <sup>f</sup>	31.68	1433	PR and RS	CS	nd
			H3N8 <sup>g</sup>	42.91				
2	Loureiro et al. 2002	K/H	H3N8 <sup>a</sup>	29.7	242	RJ	CS	nv
3	Silva et al. 1999	ND	H3N8 <sup>a</sup>	30	50	MT and MS	CS	nd
			H3N8 <sup>e</sup>	42				
4	Mancini et al. 2004	He/K/H	H3N8 <sup>d</sup>	33.33	9	SP	CS	nv
			H7N7 <sup>c</sup>	55.55				
5	Oliveira et al. 2005	K/H	H3N8 <sup>a</sup>	35.9	1106	RJ	CS	nv
6	Diel et al. 2006	He/K	H3N8 <sup>b</sup>	65.4	1506	RS	CS	nd
7	Pena et al. 2006	He/K/H	H3N8 <sup>b</sup>	35.79	514	PA	CS	nv
8	Aguiar et al. 2008	ND	H7N7 <sup>c</sup>	19.9	176	RO	SPr	nv
			H3N8 <sup>d</sup>	42				
9	Heinemann et al. 2009	He/K/H	H7N7 <sup>c</sup>	55.6	81	PA	SPr	nv
			H3N8 <sup>d</sup>	76.5				
10	Cunha et al. 2009	OIE	H7N7 <sup>c</sup>	2.7	163	SP	SPr	nv
			H3N8 <sup>d</sup>	11				
11	Filippsen et al., 2012	K/H	H3N8 <sup>d</sup>	54	37	PA, RN and SP	CS	nd
12	Filippsen, 2013	RDEH	H7N7 <sup>c</sup>	91.66	84	SP	CS	nv
			H3N8 <sup>d</sup>	100				
			H3N8 <sup>d</sup>	90.04	208	RN	nd	
13	Mancini et al., 2014	K/H	H7N7 <sup>c</sup>	98.6	72	SP	CS	nv
			H3N8 <sup>d</sup>	97.22				
14	Silva et al., 2014	K/H	H3N8 <sup>d</sup>	45.2	529	MT	SPr	nv

Source: Mori et al. (2012) with adaptations by Filippsen (2013) and Favaro; Richtzenhain (2015)

Legend: a: A/eq/2/Miami/63; b: A/eq/Santa Maria/2/88; c: A/eq/SP/56; d: A/eq/SP/1/85; e: A/eq/Fontainbleau/2/1989; f: A/eq/RJ/76; g: A/eq/GB/69; CS: Convenience sampling; P: potassium periodate; D: Dextrose; RDEH: receptor-destroying enzyme (RDE) followed by adsorption of red blood cells; SPr: Sampling to estimate seroprevalence; OIE: described as recommended by the World Organisation for Animal Health; He: 56°C heat for 30 min.; K: kaolin; H: adsorption with red blood cells; nd: not described; nv: not vaccinated

In a study on estimated prevalence in the city of Uruará, state of Pará, conducted in 1998, 81 serum samples from horses were analyzed to quantify HI antibodies against H7N7 (A/equi/SP/1/1956) and H3N8 (A/equi/SP/1/1985). The prevalence found were

55.6% and 76.55%, respectively (HEINEMANN et al., 2009).

Hemagglutination Inhibition (HI) titers against H3N8 and H7N7 were found in sera from unvaccinated horses in northern and northeastern

Brazil, comprising 1344 and 718 animals, respectively. The titers found were between 41.22% (H3N8) and 77.75% (H7N7) in the north and 24.79% (H3N8) and 30.64% (H7N7) in the northeast (PAGANO et al., 1985).

In Brazil, simultaneous detection of HI antibodies against the H3N8 and H7N7 subtypes of EIV has been described since 1985 (PAGANO et al., 1985; MANCINI et al., 2004; AGUIAR et al., 2008; HEINEMANN et al., 2009; CUNHA et al., 2009; FILIPPSEN, 2013; MANCINI et al., 2014). Among these studies, only in Rondônia (AGUIAR et al., 2008), Pará (HEINEMANN et al., 2009) and São Paulo (CUNHA et al., 2009) was a programmed sampling used in order to make inferences about seroprevalence, thereby revealing different results.

In the literature, studies on HI antibodies against the H3N8 and H7N7 subtypes of EIV conducted in São Paulo have revealed serum frequencies for H3N8 and H7N7 of, respectively, 11.0% and 2.7% (CUNHA et al., 2009); 33.33% and 55.55% (MANCINI et al., 2004); 100% and 91.66% (FILIPPSEN, 2013); and 97.22% and 98.6% (MANCINI et al., 2014).

The discrepancy between frequencies can be explained by the sampling procedures performed, which were for prevalence estimation (CUNHA et al., 2009) or for convenience (MANCINI et al., 2004; FILIPPSEN, 2013).

Although the H7N7 subtype, which is less pathogenic than H3N8, has not been isolated in the world since 1980 (WEBSTER, 1993), H7 (HI) antibodies have been detected in unvaccinated horses in other countries (WEBSTER, 1993; MADIC, 1996; OLUSA et al., 2010; DIAZ-MENDEZ et al., 2010).

In Brazil, H7 antibodies have also been reported by different authors (PAGANO et al., 1985; MANCINI et al., 2004; AGUIAR et al., 2008; HEINEMANN et al., 2009; CUNHA et al., 2009; FILIPPSEN, 2013; MANCINI et al., 2014) with positive results and frequencies of between 2.7% to 98.6%.

Absence of cross-reaction between viral subtypes H3 and H7 in the HI test has been described (TUMOVÁ; PEREIRA, 1968; CUNHA et al., 1986; LEE; SENNE; SUAREZ, 2006), but cross-reactions to other influenza A viruses can occur (TUMOVÁ; PEREIRA, 1968). Thus, given that the avian influenza virus is capable of crossing barriers between species to infect new hosts (HORIMOTO; KAWAOKA, 2001), including horses (GUO et al., 1992), it is possible to speculate that H7 antibody titers may be obtained from infection of horses by H7 subtypes other than the equine H7N7 (OLUSA et al., 2010).

Mancini et al. (2004) showed that 13 horses vaccinated against H7N7 and H3N8 and nine unvaccinated horses had antibody titers (HI) against the human H1N1 virus (A/SP/1/91), H3N2 virus (A/SP/2/95) and influenza B viruses that are restricted to humans, thus suggesting the possibility that horses might become infected with human influenza A and B.

In a study that applied a convenience sampling comprising unvaccinated equine sera from São Paulo between 2008 and 2012, the frequencies of HI titers against equine subtypes of H3N8 (A/equine/Sao Paulo/1.19/2012) and H7N7 (A/equi/SP/1/56) were compared. Higher frequency against H3N8 was confirmed ( $p < 0.05$ ), along with virus circulation in those animals (FILIPPSEN, 2013).

The donkey population in Brazil is 902,716 and the mule population is 1,221,756 (IBGE, 2013). However, only a few studies have described the presence of HI antibodies against the equine influenza virus in these animals (PAGANO et al., 1985; FILIPPSEN, 2013).

Pagano et al. (1985) reported seropositive rates of 17.17% for H3N8 (A/equi2/GB/1969) and 19.08% for H7N7 (A/equi1/RJ/1976) in donkeys (out of 262 animals) in the states of Pará and Ceará, whereas Filippsen (2013) found a seropositive rate of 88.51% for H3N8 (A/equine/Sao Paulo/1.19/2012) (out of 174 animals), in HI tests using serum samples from the state of Rio Grande do Norte.

Through compilation of the serological and virological data, it is possible to conclude that H3N8 and H7N7 equine influenza viruses circulate in the equine population in Brazil.

The number of studies on EIV characterization in Brazil is very small, with the exception of HA and NA molecular analysis on an EIV from a Brazilian

outbreak in 2012 (VILLALOBOS et al., 2013; FILIPPSEN et al., 2015).

Further studies on EIV characterization should be conducted in order to carry out surveillance on virus variants in the different regions of Brazil, thus allowing improvement of surveillance and constant vaccine updates.

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