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Genetic Divergence Between Circulating Foot-and-Mouth Disease "FMD" A, O, and SAT-2 Serotypes and Vaccine Strains in Egypt (2000-2022): A Meta-Analysis

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Abstract | This meta-analysis investigates the genetic diversity of circulating foot-and-mouth disease virus (FMDV) serotypes O, A, and SAT-2 in Egypt, alongside the vaccine strains employed for disease control from 2000 to 2022. FMD remains endemic in Egypt, causing significant economic losses in livestock production through reduced animal productivity and trade restrictions. A systematic literature review and meta-analysis synthesized data from 32 studies identified through searches of PubMed, Embase, and Web of Science databases. Studies focusing on genetic diversity of circulating O, A, and SAT-2 serotypes and vaccine strains published between 2000 and 2022 were included. The meta-analysis identified high genetic diversity among all three serotypes circulating in Egypt. Serotype O demonstrated multiple lineages and topotypes throughout the study period, while serotype A exhibited significant genetic divergence with 26 genotypic lineages and approximately 24% difference between intercontinental topotypes. SAT-2, first detected in Egypt in 2012, belongs to lineage VII and topotypes I and II. Critical findings revealed a substantial mismatch between vaccine strains and circulating field viruses vaccines containing A/Iran-05 provided only 20-40% protection against the A/Africa/G-IV variant that emerged in 2012. Field isolates demonstrated up to 6.5% genetic divergence from vaccine strains, concentrated in the major antigenic sites of the VP1 protein. Livestock data indicated a general increase in cattle production from 2000-2018, followed by sharp declines in both cattle and buffalo populations from 2018-2020. Approximately 98% vaccines' antigenic 146S/RNA complex loss occurring within four weeks under improper storage conditions, which led to lower the 146S/RNA content than international standards. The persistent genetic diversity of FMDV in Egypt, combined with vaccine strain-field virus mismatch and reduced vaccine potency, explains continued FMD outbreak occurrence despite vaccination coverage of approximately 80%. Continuous surveillance and regular vaccine strain updates are essential for effective FMD control in Egypt.

Keywords | Meta-analysis, FMD, FMDV, Maternal immunity, Circulating O, A, and SAT-2 serotypes, Egypt, FMD Vaccine, Immunity, Epidemiology

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INTRODUCTION

Foot-and-mouth disease is a highly contagious viral disease that affects cloven-hoofed animals, including livestock such as cattle, pigs, sheep, and goats. The disease is caused by the foot-and-mouth disease virus, a small, non-enveloped, single-stranded RNA virus belonging to the *Aphthovirus* genus of the *Picornaviridae* family (Metwally *et al*., 2023; WOAH, 2024). FMD is regarded as the main cause of economic loss in the dairy and beef industries in endemic nations and the main obstacle to international trade in animals and animal products. The virus is extremely contagious, and outbreaks have occurred in most of the world, currently present in every continent except North America and Australia beside UK. FMD can have a severe economic impact, resulting from poor animal yields, bans on livestock exportation, and expenses involved in eradication and control, as well as a distressing social and psychological toll on those affected (WOAH, 2024; WRLFMD, 2024). The prevalence of FMD in Egypt has been a longstanding concern as, FMD is an endemic disease, and the country has experienced numerous outbreaks over the years. This meta-analysis aims to investigate the genetic diversity of the circulating O, A, and SAT-2 serotypes of the FMD virus in Egypt, as well as the genetic diversity of the vaccine strains used to control the disease (WRLFMD, 2024).

The FMD virus is highly infectious and affects cloven-hoofed animals, including livestock such as cattle, pigs, sheep, and goats. The disease has severe economic consequences, resulting in poor animal yields, restrictions on livestock trade, and high costs associated with eradication and control efforts (Singh *et al*., 2014). FMD is endemic in Egypt, and the country has experienced numerous outbreaks over the years (Jackson, 2012).

FMD has been recorded in Egypt since 1950, when serotypes SAT-2, O, and A were identified. Serotype A and SAT-2 were the main causes of outbreaks during 1953, 1958 and 1960 (Aidaros, 2002; Zahran, 1961).

FMDV type O and A were first isolated from cattle in Egypt in 1966 and 1967, respectively. From then on serotype O was the only virus circulated in livestock until 2006. Similarly, the A serotype also exhibited significant genetic diversity, with multiple lineages and topotypes reported. serotype A is classified into 3 topotypes including Asia, Europe-South America (Euro-SA), and Africa (Aidaros, 2002; Moussa *et al*., 1979; OIE-FAO, 2000; Omar *et al*., 1985; Saber *et al*., 1997; WRLFMD, 2024).

FMDv is endemic in all Eastern Mediterranean countries including Egypt (Kitching *et al*., 1989; Moussa *et al*., 1979). FMD type O1 was responsible for several outbreaks occurred in Egypt at 1972, 1980, 1987, 1993 and 2000 (Daoud *et al*., 1988; OIE-FAO, 2000; Shawky *et al*., 2013; Shawky *et al*., 2001).

OIE reported that an outbreak of FMD in Fayoum governorate in Egypt in September 2000 typed as O1 and cattle and sheep were affected. This indicated that the virus is still being actively transmitted within livestock (OIE-FAO, 2000).

In January 2006, the clinical signs of FMDv were observed among bulls imported from Ethiopia into quarantine station at Ismailia Governorate, then occurred among local cattle, buffaloes and dairy farms in most governorates in Upper and Lower Egypt with 100% morbidity and high mortality reach to 80% in newly born calves. The virus isolated from imported and local animals was identified in Egypt as serotype A, using double Sandwich ELISA and this was subsequently confirmed by WRL-FMD in Pirbright (United Kingdom). FMD-WRL added that type A/Egypt/1/2006 virus was antigenically related to serotype A FMDv virus isolated from Ethiopia, Kenya, Yamen and Saudi Arabia. Accordingly, the obtained results suggested that type A virus may have been introduced into Egypt through live animal importation (Abd El-Rahman *et al*., 2006a, b; WRLFMD, 2024).

The characterization of FMD serotype A virus responsible for Egypt 2006 outbreaks was done by Knowles *et al*. (2007). Phylogenetic analysis of VP1 nucleotide sequences demonstrated a close relationship to recent FMD virus isolates from East Africa (African topotype), rather than to viruses currently circulating in the Middle East (Habiela *et al*., 2010; Hagag *et al*., 2019; Knowles *et al*., 2009).

FMD serotype A virus antigen was detected by indirect sandwich ELISA in 8 samples out of 15 epithelial tissue samples from 90 infected animals (60 infected cattle and 30 infected buffaloes). The samples collected from three private farms at Gharbia Governorate. They succeeded in isolating the virus on BHK-21 cells from 5 samples out of 8 samples (positive by indirect Sandwich ELISA) (Knowles *et al*., 2007, 2009; WRLFMD, 2024).

In 2012 a devastating FMD virus SAT-2 outbreak had emerged in most Egyptian governorates with high morbidities and mortalities in calves, The lack of antibodies against FMD virus SAT-2 made the animal's highly susceptible and virgin soil for the newly introduced FMD outbreak. The rapidly spreading nature of FMD SAT-2 type resulted in great losses in intensive livestock production system. Producers demanded a governmental control program to prevent such devastating FMD outbreak (Ahmed *et al*., 2012; WRLFMD, 2024).

Previous studies have investigated the seroprevalence and risk factors associated with FMD in various regions. Regional studies have also highlighted the challenges and prospects for the control of FMD in Africa. livestock production is severely affected by the widespread distribution of animal diseases, with FMD being a major constraint to productivity in Ethiopia. in southern Africa, FMD had a detrimental effect on the agricultural economies of most of the country, with direct economic losses associated with reduced livestock products estimated at US$2.3 billion per year (FAO, 2024; Shurbe *et al*., 2022; WRLFMD, 2024).

Another study in Southern Africa analyzed FMD outbreaks from 2014 to 2018, highlighting the detrimental impact of the disease on agricultural economies (Fana *et al*., 2021). The genetic diversity of the circulating FMD virus strains and the vaccine strains used to control the disease is an important factor in the continued management of the disease.

Egypt's FMD control relies on routine prophylactic vaccination, using a trivalent vaccine targeting the endemic serotypes O, A, and SAT-2. Specific local strains are included due to viral diversity, such as O Pan-Asian II (EGY/2010), A Iran 05 (A/EGY/1/2012), and SAT-2 strains like EGY/Gharbia/2012 and LIB/2018. The A G-IV isolated from 2020 (MW413350) was also incorporated. Despite these efforts, outbreaks persist due to poor vaccine matching and high genetic variation. For instance, circulating strains like the 2022 A/African G-IV exhibited 10% to 17% divergence from vaccinal strains like A Iran-5 Egypt-2012, highlighting the frequent issue of vaccine inefficacy (Nahas and Salem, 2020; Shahein *et al*., 2023; WRLFMD, 2024).

MATERIALS AND METHODS

This meta-analysis reviews the available literature on the genetic diversity of the circulating O, A, and SAT-2 serotypes of the FMD virus in Egypt, as well as the genetic diversity of the vaccine strains used to control the disease, from 2000 to 2022. The search was conducted using various scientific databases, including PubMed, FAO, WRLFMD, and Web of Science, using keywords such as foot-and-mouth disease, genetic diversity, Egypt, and the specific serotypes (O, A, and SAT2) ["foot-and-mouth disease" AND "genetic diversity" AND "Egypt" AND ("O serotype" OR "A serotype" OR "SAT-2" OR "SAT2 serotype"].

The inclusion criteria for the studies were:
First, the studies must focus on the genetic diversity of the circulating O, A, and SAT-2 serotypes of the FMD virus in Egypt, or the genetic diversity of the vaccine strains used to control the disease.
Second, the studies must have been published between 2000 and 2024.

Data extraction included information on the study location, sample size, sampling period, laboratory techniques used for virus identification and characterization, and the genetic diversity of the identified virus strains.

Meta-analysis was conducted to synthesize the available data and provide an estimate of the genetic diversity of the circulating FMD virus serotypes and vaccine strains in Egypt over the study period.

RESULTS

The initial literature search identified 623 relevant articles, of which 32 met the inclusion criteria for this meta-analysis. The included studies reported on the genetic diversity of the circulating O, A, and SAT-2 serotypes of the FMD virus in Egypt between 2000 and 2022. The meta-analysis of the included studies showed that the predominant circulating serotypes in Egypt during the study period were O, A, and SAT-2 as summarized in Table 1 and 2. The genetic diversity of the circulating O serotype was high, with multiple lineages and topotypes identified across the different studies.

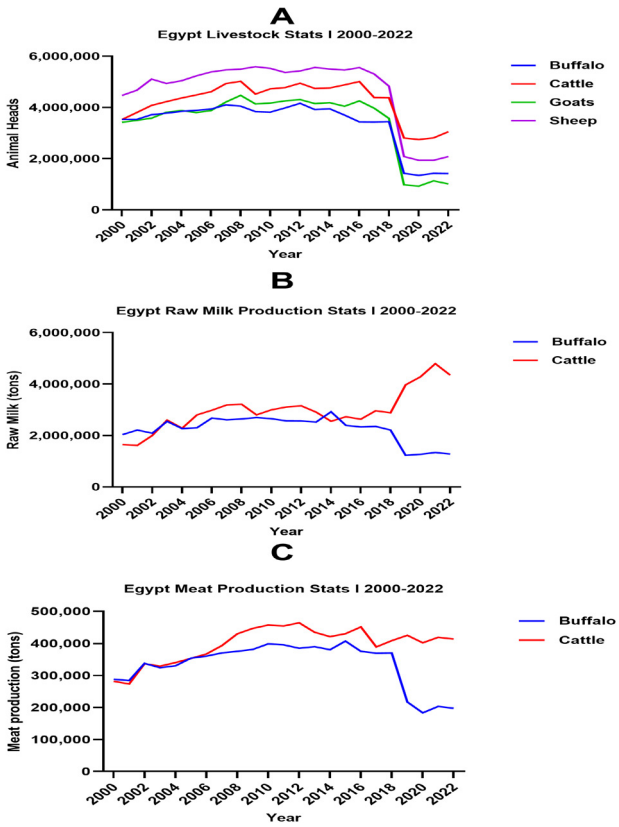

Figure 1: The graphs depict Egypt's livestock statistics (A), raw milk production (B), and meat production from 2000 to 2022 (C) for various animals, with a focus on cattle and buffalo (FAO, 2024) Created Using GraphPad Prism 10.

The graphs depict Egypt's livestock statistics, raw milk production, and meat production from 2000 to 2022 Figure 1 (FAO, 2024). In terms of livestock count, both cattle and buffalo populations showed a general increase from 2000 to around 2018, with cattle numbers slightly higher than buffalo. However, there was a sharp decline in both populations from 2018 to 2020, followed by a slight recovery by 2022. This may be due to FMD outbreak effect and control strategy effect. Cattle numbers remained higher than buffalo throughout the period. Raw milk production trends differed significantly between cattle and buffalo. Buffalo milk production remained relatively stable with a slight increase from 2000 to 2018, then dropped sharply. In contrast, cattle milk production showed a more dramatic increase, especially from 2016 onwards, surpassing buffalo production and reaching peak levels by 2022.

Meat production for both cattle and buffalo increased steadily from 2000 to 2018, with cattle consistently producing more meat than buffalo. After 2018, there was a sharp decline in buffalo meat production, while cattle meat production experienced a less severe drop followed by stabilization. By 2022, cattle meat production was significantly higher than buffalo meat production. These trends suggest a shift in Egypt's livestock industry, with cattle gaining prominence in both milk and meat production, while buffalo numbers and production have declined in recent years.

In Africa, the livestock count for cattle showed a steady increase over the years, while buffalo numbers remained relatively stable until 2018, after which there was a sharp decline. In Asia, both cattle and buffalo populations increased gradually, with cattle numbers slightly higher than buffalo (FAO, 2024).

Milk production in Africa for cattle demonstrated consistent growth, rising from about 20 million tons in 2000 to over 40 million tons by 2022. Buffalo milk production in Africa remained relatively constant until 2018, then declined sharply. In Asia, both cattle and buffalo milk production increased significantly, with cattle milk production showing a more dramatic rise, surpassing buffalo milk production around 2010 and reaching nearly 30 million tons by 2022.

Regarding meat production, Africa saw a steady increase in cattle meat production, rising from about 4 million tons in 2000 to nearly 7 million tons by 2022. Buffalo meat production in Africa remained relatively stable until 2018, then dropped sharply. In Asia, both cattle and buffalo meat production increased, with cattle meat production showing a steeper rise, reaching about 1.5 million tons by 2022, while buffalo meat production grew more modestly to about 0.5 million tons.

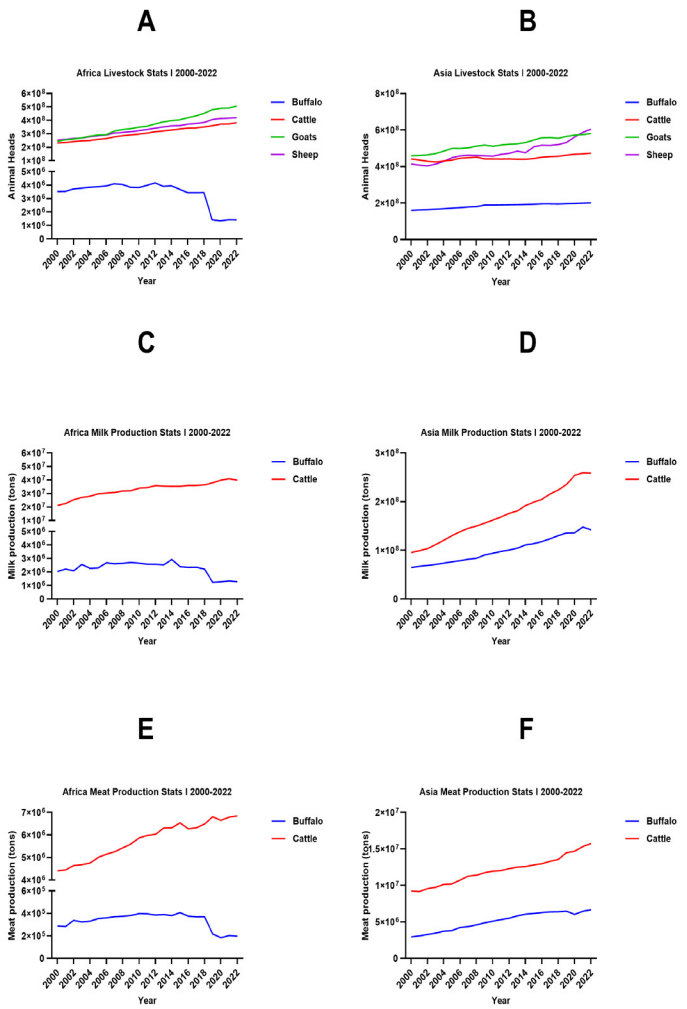

Figure 2: The graphs depict Africa's and Asia's livestock statistics (A and B), raw milk production (C and D), and meat production from 2000 to 2022 (E and F) for various animals, with a focus on cattle and buffalo (FAO, 2024) Created Using GraphPad Prism 10.

Overall, these trends indicate a general growth in cattle-related production in both continents, while buffalo production showed mixed results, with more stability in Asia and a decline in Africa in recent years.

Egypt Status Summary from WRLFMD updated 2024 summarized in Table 1 and 2. (FAO, 2024; WOAH, 2024; WRLFMD, 2024).

Table 1: Egypt status summary from WRLFMD updated 2024 (WOAH, 2024; WRLFMD, 2024).

Serotype	Years
Untyped:	2008, 2009, 2011-2015, 2017, 2018
FMDV-O:	1951, 1958, 1961-1962, 1964-1977, 1978-1982, 1987, 1989-1994, 1997, 2000, 2006-2009, 2011-2017, 2021, 2022
FMDV-A:	1952 (or 1953?), 1956, 1958, 1972, 2006, 2009-2013, 2015-2018, 2020-2022
FMDV-SAT-2:	1950, 2012, 2014-2018

Table 2: Year distribution of FMDV serotypes and vaccine strains in Egypt (GenBank and WRLFMD Data (WOAH, 2024; WRLFMD, 2024).

Year\ Source	Serotype A (GenBank)	Serotype A (WRLFMD)	Serotype O (GenBank)	Serotype O (WRLFMD)	SAT-2 (GenBank)	SAT-2 (WRLFMD)	Vaccine strains (WRLFMD)	Notes
2006	0	5 EGY/1/2006 EGY/2/2006 EGY/3/2006 EGY/4/2006 EGY/5/2006	0	1 EGY/8/2006	0	0		
2007	0	3 EGY/6/2006 EGY/7/2006 EGY/9/2006	0	8 EGY/8/2006 EGY/25/2007 EGY/26/2007 EGY/27/2007 EGY/28/2007 EGY/29/2007 EGY/30/2007 EGY/31/2007	0	0		
2008	0	0	0	5 EGY/1/2008 EGY/3/2008 EGY/4/2008 EGY/5/2008 EGY/7/2008	0	0		Untyped samples also reported in 2008
2009**	0	9 EGY/3/2009 EGY/4/2009 EGY/7/2009 EGY/9/2009 EGY/12/2009 EGY/13/2009 EGY/14/2009 EGY/15/2009 EGY/16/2009	6 KC565751.1 KC565750.1 JQ837836.1 JQ837835.1 JQ837834.1 JQ837833.1	19 EGY/1/2009 EGY/6/2009 EGY/8/2009 EGY/17/2009 EGY/18/2009 EGY/19/2009 EGY/20/2009 EGY/21/2009 EGY/22/2009 EGY/23/2009 EGY/24/2009 EGY/25/2009 EGY/26/2009 EGY/27/2009 EGY/28/2009 EGY/29/2009 EGY/30/2009 EGY/31/2009 EGY/32/2009	5* JX570630.1 JX570630.1 JX570630.1 JX570629.1 JX570628.1	0		Untyped samples also reported in 2009
2010**	0	3 EGY/1/2010 EGY/2/2010 EGY/3/2010	2* KC565753.1 KC565752.1	0	0	0		
2011	1 KC888939.1	4 EGY/2/2011 EGY/5/2011 EGY/8/2011* EGY/9/2011	0	3 EGY/6/2011* EGY/7/2011 EGY/10/2011*	0	0		Untyped samples also reported in 2011-2015
2012	0	4 EGY/1/2012 EGY/18/2012* EGY/20/2012 EGY/30/2012*	1 DQ164871.1	12 EGY/6/2011* EGY/7/2011 EGY/10/2011* KC440883.1 EGY/19/2012* EGY/26/2012 EGY/27/2012* EGY/19/2012 EGY/25/2012 EGY/27/2012	17 JX570617.1* JX570627.1 KF112931.1 JX013980.1 JX013979.1 KF055861.1 KF112936.1 KF112935.1 JX570626.1 JX570625.1	19 EGY/2/2012* EGY/3/2012 EGY/4/2012 EGY/5/2012 EGY/6/2012* EGY/9/2012* EGY/10/2012 EGY/11/2012 EGY/13/2012 EGY/14/2012 EGY/15/2012	O, A, SAT2 - Accession number JX570617.1 FMD- SAT2-EGY/2/2012	SAT-2 first recorded in 2012

Tables contibues on next page.....

Year\ Source	Serotype A (GenBank)	Serotype A (WRLFMD)	Serotype O (GenBank)	Serotype O (WRLFMD)	SAT-2 (GenBank)	SAT-2 (WRLFMD)	Vaccine strains (WRLFMD)	Notes
					JX570624.1 JX570623.1 JX570622.1* JX570621.1* JX570620.1 JX570619.1 JX570618.1	EGY/16/2012 EGY/17/2012 EGY/21/2012 EGY/22/2012 EGY/28/2012 EGY/29/2012 EGY/31/2012* EGY/24/2012*		
2013 **	2 KR092701.1 KJ210071.1	10 EGY/3/2013* EGY/5/2013 EGY/6/2013 EGY/11/2013 EGY/12/2013 EGY/13/2013* EGY/14/2013 EGY/15/2013 EGY/17/2013* EGY/19/2013*	1* KX258001.1	0	2* KJ210079.1 KJ210080.1	0	A - Accession numbers not provided in the source	Serotypes SAT-2 and O only reported in GenBank
2014	3 KT699212.1 KT699211.1 KX083565.1	4 EGY/30/2013 EGY/31/2013 EGY/31/2014 EGY/13/2014*	4 KT121467.1 KT121466.1 KT121465.1 KR261672.1	21 EGY/1/2014 EGY/3/2014 EGY/4/2014 EGY/5/2014 EGY/6/2014 EGY/10/2014* KX258003.1 EGY/18/2014* EGY/23/2014* EGY/25/2014 EGY/26/2014 EGY/27/2014 EGY/28/2014 EGY/29/2014 EGY/32/2014 EGY/34/2014 EGY/36/2014* EGY/31/2014 RL-440/ EGY/2014 RL-453/EGY/2014 RL-455/ EGY/2014	1 KF747340.1	6 EGY/43/2012 KX258063.1 EGY/24/2014* KX258067.1 EGY/10/2014* EGY/18/2014*		O, A, SAT-2 - Accession Number KX258003.1 O, SAT-2
2015 **	3* MG552838.1 MG552840.1 MG552837.1	0	0	6 EGY/3/2015 EGY/9/2015 EGY/10/2015 EGY/11/2015 EGY/13/2015 EGY/14/2015	0	0	No vaccine recorded in the sources for 2015	Serotype A only reported in GenBank, Serotype O only in WRLFMD records
2016	3 MG552842.1 MG552841.1 MH588713.1	1 EGY/3/2016*	9 MG571528.1 MG017365.1 MG017364.1 MG017363.1 MG017362.1 MG017361.1 MF322680.1 MF322679.1 MF322678.1	12EGY/4/2016 EGY/5/2016 EGY/7/2016* EGY/8/2016 EGY/9/2016 EGY/10/2016 EGY/11/2016 EGY/12/2016 EGY/14/2016 EGY/16/2016 EGY/17/2016 EGY/18/2016*	0	1 EGY/5/2015*	O - No accession numbers provided for this vaccine strain O, A, SAT2	Untyped samples also reported in 2017 and 2018

Tables contibues on next page.....

Year/ source	Serotype A (GenBank)	Serotype A (WRLFMD)	Serotype O (GenBank)	Serotype O (WRLFMD)	SAT-2 (GenBank)	SAT-2 (WRLFMD)	Vaccine strains (WRLFMD)	Notes
2017	0	1 EGY/19/2016*	19 MH729321.1 MH729320.1 MH729319.1 MH729318.1 MH729317.1 MH729316.1 MF322692.1 MF322691.1 MF322690.1 MF322689.1 MF322688.1 MF322687.1 MF322686.1 MF322685.1 MF322684.1 MF322683.1 MF322682.1 MF322681.1 LC384395.1	22 EGY/4/2017 EGY/6/2017 EGY/7/2017 EGY/8/2017 EGY/9/2017 EGY/10/2017* EGY/11/2017 EGY/13/2017 EGY/16/2017 EGY/17/2017 EGY/19/2017 EGY/21/2017 EGY/22/2017 EGY/25/2017 EGY/26/2017 EGY/27/2017 EGY/28/2017 EGY/30/2017 EGY/31/2017 EGY/32/2017 EGY/33/2017	0	1	O, A	Untyped samples also reported in 2017 and 2018
2018	2 MH732982.1 MH732983.1	2 EGY/2/2018	0	1 EGY/34/2017	0	6 EGY/1/2018 EGY/7/2018 EGY/19/2018 EGY/21/2018 EGY/31/2018 EGY/34/2018	O, A, SAT-2- Accession Numbers MT863268, MT602079	Untyped samples also reported in 2017 and 2018. The 2018 vaccine includes isolates from Egypt and Sudan. The source also states that the 2020 vaccine in Egypt includes "serotype O Pan-Asian II (EGY/2010), A Iran 05 (A/EGY/1/2012)".
2019	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited.
2020	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited. The 2020 vaccine includes isolates from Egypt, Iran, and potentially Liberia, based on this and other information from the source.
2021	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited.
2022	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited.
2023	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited.
2024	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Data from the sources for 2019-2024 is limited.

Table presents the year distribution of FMDV serotypes O, A, and SAT2, along with the recorded vaccine strains used in Egypt, based on data from GenBank and WRLFMD. *: The serotype was recorded in GenBank but missing in WRLFMD data. *: Vaccine strains, **: Serotypes with missing records in WRLFMD and missed vaccine program.

Table 2 highlights some of the discrepancies and data gaps between the two sources, GenBank and WRLFMD, which are acknowledged in the source materials. For example, the absence of SAT-2 records in the WRLFMD database for 2009, despite their presence in GenBank, is noted. Such inconsistencies underscore the importance of considering multiple data sources for a comprehensive understanding of FMDV epidemiology. Additionally, the Tables 1 and 2 shows that WRLFMD provides information about the specific vaccine strains used in certain years, which is not available in the GenBank data. This information on vaccine usage is crucial for assessing vaccine effectiveness and guiding vaccination strategies. The primary issue confronting FMD control is Vaccine Mismatch due to the constant genetic diversification of the virus, which renders existing vaccine strains ineffective due to a lack of cross-protection, even within the same serotype. 1: Genetic Distance: Phylogenetic analyses have repeatedly shown that vaccine strains are genetically distant from the strains actively circulating during outbreaks. The O vaccine strain (KX258003.1) used in 2014 was phylogenetically "located far from the other virus strains of that year". One SAT-2 vaccine strain (JX570617.1) was placed in a different subclade, far from the circulating virus strains analyzed between 2012 and 2018. Amino Acid Substitutions: Significant genetic variation was observed between isolates and vaccine strains, associated with up to 26 amino acid substitutions. The accumulation of mutations at the immunogenic G-H loop site can cause antigenic shift, leading to invalid vaccination. Recent Serotype A Mismatch (2022): The 2022 circulating Serotype A African G-IV strain showed substantial divergence from existing vaccine components: It exhibited an identity percentage of only 84.55±0.82% with the vaccinal strain A Iran-5 Egypt-2012 and 82.99±0.8% with the Iranian-2005 strain. There was a notable 9.3% divergence compared to the local vaccinal strain isolated in 2020. Overall divergence with vaccinal strains ranged from 10 to 17%. This lack of genomic expression similarity is cited as a reason for disease outbreaks occurring despite vaccination. The sources conclude that a different strategy for vaccine serotype selection is needed, and that the current 2022 Serotype A African G-IV isolate should be rapidly incorporated into the authorized vaccine to ensure proper coverage against emergent African topotypes (Nahas and Salem, 2020; Shahein *et al*., 2023; WRLFMD, 2024).

The A-type was found to disseminate in various epidemic spots (epicenters) throughout the Egyptian governorates including Cairo, Giza, Kafr El-Sheik, Al-Menofia, Kalyoubia, Daqahlyia, Al-Behera, and Al-Gharbia from Nile Delta. Beni-Suwayf, AlFayyum, Asyut from Central Egypt, Suhag, El-Menya, Aswan from Upper Egypt, and El-Wadi El-Gadid from Western Egypt. Meanwhile, A-IranO5-08 (Iranian strain) was identified in 2010 and recorded during 2013–2015. Besides, the African type-G-IV was first recorded in 2012 with the recorded lab investigation in 2016, 2018, and 2020 (Habiela *et al*., 2010; Hagag *et al*., 2019).

Based on the nucleotide sequences and genetic analysis, more than 15% of genetic difference in viral protein 1 (VP1), the serotype A virus assorted to 26 genotypic lineages beside and around 24% difference between different intercontinental topotypes. Euro-Asian serotypes as in the seventies of this century, the genetic diversity was about 32 subtypes discriminated. Moreover, the Asian topotype is most rife in the Middle-East and South-Asian sectors with the identified lineages including A15, A22, A-IRN99, A-Iran05, A-IRQ24,46, A-TUR2006, etc. In the West-Eurasian district, the dominance is related to the A-Iran 05 lineage. The recorded sequence analysis of the virus capsid indicated that serotype A, the African type was subdivided into well-identified genotypes (I, II, IV, and VII). In Egypt, serotype A was first isolated in the sixties of the last century till the massive outbreak struck the country in 2006 with the relative nucleotide homology between the Egyptian and the East-African types.

The meta-analysis also revealed that serotype SAT2 of the FMD virus was first detected in Egypt in 2012, during an outbreak affecting cattle, sheep, and buffalo. The SAT-2 serotype was found to be genetically diverse, with multiple lineages and topotypes identified over the study period. The genetic characterization of the SAT2 viruses isolated in Egypt from 2012 to 2024 revealed that they belong to the lineage VII and Topotypes I and II. The SAT2 serotype, although less prevalent than the O and A serotypes, also showed a moderate level of genetic diversity, with multiple lineages identified. Regarding the vaccine strains, the studies reported that the vaccine strains used in Egypt did not always match the genetic profiles of the circulating field strains, which may have contributed to the continued occurrence of FMD outbreaks in the country.

DISCUSSION

Foot-and-mouth disease (FMD) is a highly contagious viral disease that affects cloven-hoofed animals, including livestock such as cattle, sheep, and pigs. The disease is characterized by fever, blisters on the tongue, lips, and feet, and can lead to severe economic losses for agricultural production systems (Yang *et al*., 2014). In Egypt, the epidemiology of foot-and-mouth disease outbreaks has been a significant concern for the livestock industry, with recurring outbreaks reported over the past two decades (Dahiya *et al*., 2020).

From 2006 to 2023, Egypt has experienced multiple outbreaks of foot-and-mouth disease, with the virus affecting a wide range of livestock species. The disease is caused by the *Aphthovirus*, a member of the *Picornaviridae* family, which has several serotypes, including A, O, C, SAT1, SAT2, SAT3, and Asia 1 (Ahmed *et al*., 2012, 2018; Grubman and Baxt, 2004; Rodriguez *et al*., 2020). The serotype variability of the virus means that the immune response is sero-specific, and vaccines must be designed to protect against each serotype independently.

Studies have shown that the prevalence of foot-and-mouth disease in Egypt has been influenced by various factors, including the introduction of new viral strains, the movement of livestock, and the effectiveness of control measures implemented by the government and veterinary authorities (Grubman and Baxt, 2004; Rodriguez *et al*., 2020; Sangula *et al*., 2010; Yang *et al*., 2014; Yousef *et al*., 2025). The spread of the disease is typically controlled through measures such as movement restriction, stamping-out policies, pre-emptive culling, and emergency vaccination (Bastos *et al*., 2003).

Vaccine formulations in Egypt

Egypt employs multiple foot-and-mouth disease vaccine formulations to combat the persistent endemic circulation of FMDV serotypes O, A, and SAT-2. The vaccination strategy utilizes locally produced trivalent inactivated oil-adjuvant vaccines alongside imported polyvalent formulations. The locally produced vaccines contain serotypes derived from Egyptian isolates, specifically O Panasia-2, A Iran-05, and SAT-2 variants. These chemically inactivated vaccines consist of intact viral particles selected to match circulating viruses in the region (Bastos *et al*., 2003; Yousef *et al*., 2025).

Modern vaccine preparations have been expanded to include broader serotype coverage. A heptavalent formulation now incorporates A-Iran-05, A-Africa G-IV (2022), A-Europe SA, O-PanAsia-2, O-Manisa 69, O-EA3, and two SAT-2 variants, providing enhanced protection across multiple topotypes. Additionally, tetravalent formulations containing strains targeting Middle Eastern and African circulation patterns have demonstrated immunogenicity against 22 lineages prevalent in targeted regions. The Egyptian vaccination campaign operates with three massive vaccination programs annually since 2017, achieving approximately 80 percent vaccination coverage across susceptible species including cattle, sheep, and goats.

Vaccination failure in Egypt stems from multiple interconnected factors. The primary cause remains antigenic strain mismatch between vaccine formulations and circulating field viruses. Beginning in 2012, the Africa G-IV lineage emerged in Egypt, creating significant protection gaps. When the 2022 outbreak occurred with the A/Africa/G-IV variant, sera from vaccinated animals showed inadequate cross-protection, with serological r1-values of only 0.235 and 0.243 for local and imported vaccines respectively. Challenge studies demonstrated protection levels of merely 20 percent and 40 percent against this variant, compared to 80-100 percent protection against the vaccine-matched A/Iran-05 strain (El-Bagoury *et al*., 2015; Yousef *et al*., 2025).

Genetic variation in immunologically critical viral regions presents another critical challenge. Recent FMD isolates demonstrate up to 6.5 percent genetic divergence from vaccine strains, with substantial variation concentrated in the VP1 protein major antigenic sites. This low-fidelity RNA polymerase of FMDV enables rapid viral evolution, particularly under immune pressure from partially vaccinated populations. Recombination events have been documented between serotypes, further complicating vaccine matching efforts (Abd-Ellatieff *et al*., 2023).

Vaccine potency and antigen payload insufficiency contributes significantly to vaccination failure. Analysis of some Egyptian vaccines revealed considerably lower FMDV 146S/RNA content compared to international standards, suggesting suboptimal antigenic mass. The required protective virus-neutralizing antibody titer threshold of 1.65 $\log_{10}$ is frequently not achieved, particularly against heterologous strains. Storage conditions and cold-chain integrity affect vaccine stability, with approximately 98 percent of FMDV antigenic 146S/RNA complex lost within four weeks when stored improperly cold chain process (Ahn *et al*., 2021; Kim *et al*., 2024).

Additional factors/elements include maternally derived antibody interference in young animals, short duration of safety necessitating repeated boosters, insufficient vaccination coverage, and variable strain Passage No. for production performance. The obligatory vaccination applications, while enhancing herd immunity, paradoxically create selective pressure for vaccine-break out editions. This phenomenon underscores the dynamic nature of FMD epidemiology in endemic areas like Egypt, in which continuous antigenic surveillance and vaccine reformulation remain crucial for outbreak prevention and manipulate.

The results of this meta-analysis highlight the significant genetic diversity of the circulating FMD virus serotypes in Egypt, particularly the O, A, and SAT-2 serotypes. The high level of genetic diversity observed in the circulating strains and the potential mismatch between the vaccine strains and field strains may explain the continued

occurrence of FMD outbreaks in the country, despite ongoing vaccination efforts (Sinkala *et al*., 2012).

The findings of this study underscore the importance of continuous monitoring and characterization of the FMD virus strains circulating in Egypt, as well as the need to regularly update the vaccine strains to ensure better alignment with the field strains. Despite providing a comprehensive overview, this meta-analysis has certain limitations. Its reliance on published literature means it could be subject to publication bias, potentially overlooking studies with non-significant findings or those not available in indexed databases. Variances in methodologies, sampling strategies, and diagnostic techniques across the included studies might introduce heterogeneity, affecting the comparability of genetic diversity estimates. Furthermore, while the study spans a broad period (2000-2024), data availability for specific serotypes or timeframes within this period might be uneven. Future research could benefit from standardized reporting and more extensive molecular surveillance efforts across all regions of Egypt. This meta-analysis offers a comprehensive overview of the genetic diversity of the FMD virus in Egypt. This information can be used to develop more effective control and prevention strategies to reduce the impact of FMD on the country's livestock industry.

The genetic diversity of the FMD virus in Egypt highlights the challenges in controlling the disease, as the virus can evolve quickly and potentially evade the immunity conferred by the available vaccines.

In terms of the genetic diversity of the FMD vaccine strains used in Egypt, the meta-analysis found that the vaccine strains have been updated over the years to match the circulating field strains. This meta-analysis provides a comprehensive overview of the genetic diversity of the FMD virus in Egypt, which can inform the development of more effective control and prevention strategies to mitigate the impact of the disease on the country's livestock industry (Hassan *et al*., 2022; Yousef *et al*., 2025).

CONCLUSION AND RECOMMENDATIONS

In conclusion, the meta-analysis of the available data on the genetic diversity of the circulating FMD virus serotypes and vaccine strains in Egypt from 2000 to 2022 reveals a high level of diversity, particularly for the O, A, and SAT-2 serotypes. The continued occurrence of FMD outbreaks in Egypt despite ongoing vaccination efforts may be attributed to the genetic diversity of the circulating strains and potential mismatch between the vaccine strains and field strains. Continuous monitoring and characterization of the FMD virus strains using ELISA, R-value, and Molecular techniques, as well as regular updates to the vaccine strains, ensure the vaccination coverage and efficiency, are crucial to improve the effectiveness of FMD control and prevention strategies in Egypt.

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NOVELTY STATEMENT

This a recent updated twenty years FMD meta-analysis study done in Egypt, with highlight on the need of future challenges as data availability, full sample analysis, and fostering collaboration between governmental agencies and local communities can facilitate more effective surveillance efforts and ensure timely response mechanisms are in place to address emerging FMD threats. This analysis underscores the need for different strategies in selecting vaccine serotypes to combat the genetic diversity of FMDV in Egypt.

AUTHOR'S CONTRIBUTION

Each author has made an equal contribution in offering their technical expertise and insights to develop this article.

Ethics approval

The ethical and research committee at the Faculty of Veterinary Medicine, Cairo University, approved the study protocol under reference number (CU-II-F-30-20).

Generative AI and AI-assisted technology statement

The authors declare that generative AI technologies as (chat GPT) or AI tools not utilized in any capacity during the preparation, writing, analyze, draw data or editing of this research.

Conflict of interest

The authors have declared no conflict of interest.

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