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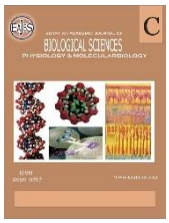

Simian Foamy Virus Responsible For Co-Infection In Human Population Setting: A Meta-Analysis Study

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ABSTRACT

The development of genome amplification assays has made it possible to describe new foamy viruses (FV) and re-evaluate the part that assists them in transmission to humans causing co-infection. To shed light on the prevalence of simian foamy virus (SFV) in hosts due to the presence of other non-human primates or cattle in nearby regions, this systematic review and meta-analysis was started. Through the databases of Pubmed and Global Index Medicus, we conducted an electronic search. We included observational studies that indicate the presence of zoonotic infection in human population settings related to SFV via cross-species transmission only. The quality of the included articles was evaluated after data extraction. Using a random effect model, we performed analyses on sensitivity, subgroups, publication bias, and heterogeneity. Out of a total of 417 studies retrieved, 12 articles were included in the systematic review. A meta-analysis, performed on 10 studies, revealed a significantly increased risk of SFV transmission in humans due to the bite, scratches, and saliva transmission from non-human primates. Through its analysis of the most recent literature, this study has the advantage of providing public health authorities with useful information about the effectiveness of current precautions against SFV.

INTRODUCTION

The Simian Foamy Virus (SFV), which belongs to *Spumaretrovirinae* is a retrovirus that infects non-human primates, including monkeys and apes. It is characterized by the formation of a distinctive "foamy" appearance when observed under an electron microscope (Huang *et al.*, 2012; Kehl *et al.*, 2013). SFV has been found in various primate species, both in captivity and in the wild. It is generally transmitted through close contact with infected animals, such as bites, scratches, or exposure to bodily fluids (Materniak-Kornas *et al.*, 2019). SFV is considered a zoonotic virus, meaning it can be transmitted from animals to humans under certain circumstances (Materniak-Kornas *et al.*, 2022). In humans, SFV infections are rare and usually associated with individuals who have occupational or frequent exposure to non-human primates, such as researchers, zookeepers, or individuals involved in the bushmeat trade. However, human-to-human transmission has not been reported (Wöhrl *et al.*, 2019; Hashimoto-Gotoh *et al.*, 2020; Schweizer *et al.*, 1997; Couteaudier *et al.*, 2022).

It's important to note that SFV is generally considered non-pathogenic in both primates and humans, meaning it does not typically cause significant disease or illness. Most infections are asymptomatic or cause mild, flu-like symptoms that resolve on their own (Calattini *et al.*, 2007). Long-term studies in individuals with SFV infections have not shown any associated health problems (Aso *et al.*, 2021). Research on SFV is ongoing to better understand its prevalence, transmission dynamics, and potential health implications (Santos *et al.*, 2019). As with any zoonotic virus, it's important for individuals who work closely with non-human primates to follow appropriate safety protocols and preventive measures to minimize the risk of infection. Over the last two decades, SFV has dramatically expanded its geographic range (Park and Mergia, 2002).

The potential occupational risk of SFV among outdoor workers is a major concern, especially for those who work in direct contact with non-human primates, according to health experts (Olszko and Trobridge , 2013; Shankar *et al.*, 2020; Clarke *et al.*, 1970). The primary objectives of this study were to assess the prevalence of SFV antibodies, review the incidence of SFV in workers, and conduct a meta-analysis to calculate the relative risk for such workers in comparison to controls. A secondary goal of this study was to identify SFV risk factors in zoo caretakers and pet owners, which would provide information for evidence-based prevention strategies.

MATERIALS AND METHODS

Using a pre-established protocol that was registered on the international prospective registry for systematic review protocols PROSPERO (registration number: CRD42021252608), we conducted this systematic review and meta-analysis.

1-Search Criteria:

We adhered to the Cochrane criteria and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher *et al.*, 2009). We looked through the English-language databases of PubMed/Medline, Web of Science, Scopus, and Google Scholar for papers that met the following requirements and were published between January 1, 1961, and March 30, 2023. Due to the limitation of available data and research articles, we have included all the data available in various databases.

2-Inclusion and Exclusion Criteria:

Case studies, observational studies, and published, peer-reviewed randomized control trials (RCTs) comprise the study design. A review of the references of the articles and reviews that were included was added to the literature search. By incorporating the precise keywords from the searches that were manually discovered, we have gradually updated our search strategy iteratively. There are no geographical or linguistic limitations. Editorials, reviews, guidelines, and press reports were all excluded from the theoretical models. Research on SFV vaccines, SFV genetics or diagnostics, neurological sequelae, knowledge and literacy, and SFV neurological sequelae are included in this meta-analysis.

The following Medical Subject Heading (MeSH) terms were used: foamy virus, simian foamy virus, zoonotic infections, co-infections, non-human primate, and serological prevalence. Further, the most sensitive search includes (zoonotic disease [MH] OR foamy virus, co-infection [MH] OR simian foamy virus, non-human primate [MH] OR simian foamy virus, foamy virus [MH] OR cross-species transmission). An earlier systematic review on important emerging zoonotic viral infections for population health settings used a similar string with success. Additionally, relevant publications that met the inclusion criteria were looked for in the reference lists of included studies.

3-Data Extraction and Assessment Bias:

The study group is divided into the following categories: (i) geographic area of the study, (ii) time of the study, and (iii) serological investigations performed. After an initial screening of the title and abstract, we

read the full text of eligible studies. Each pertinent study's data were gathered. Source (first author and year of publication), general study details (citation, study design, and year of publication), and other information were all extracted. (iii) Setting (country/region taken into account, study population compared to comparison group); (iv) Key findings of the study.

4-Meta-Analysis:

The Meta-Essentials package, version 1.5, was used to conduct the meta-analysis. Using the random effects model, the study's pooled odds ratio (OR) was determined (Suurmond *et al.*, 2017). We investigated whether there was heterogeneity among the initial studies and analyzed how the results of various studies varied (Van Rhee *et al.*, 2015; DerSimonian and Kacker, 2007). The heterogeneity indicator (I square—I^2-statistic), with I^2 values of 25%, 50%, and 75% corresponding to a small, medium, and large degree of heterogeneity, was used to assess the consistency of the results. Additionally, a visual inspection was done to check for publication bias in the five effect sizes. The funnel plot's asymmetrical shape suggested the presence of publication bias.

RESULTS

Among all retrieved 327 articles were from PubMed, 54 articles from Google Scholar papers, and 36 articles from other sources. After the removal of 182 duplicates, 231 articles were assessed for further analysis. A total number of 63 therapeutic-based studies, 12 socio-economic impact research-related articles,22 studies on genetic and clinical impact, 71 articles on other simian viruses, 24 on awareness of attitude towards, and 9 studies in non-English written articles. In the end, the concerned systematic review includes 30 studies,15 of which are included in the quantitative meta-analysis to identify the major cause of cross-species transmission of Simian foamy virus (SFV).

1-Selected Dataset:

The selected dataset includes articles highlighting the experimentation performed on several non-human primates, apes, and monkeys. In this analysis, 12 studies include serological testing experimentation in a temporal manner at different geographical locations. The concerned experiments include sample collection from zoo caretakers, butchers, pet owners, and "monkey-temple" workers. All these studies analyze the presence of antibodies against SFV in humans after infection or treatment. The remaining 3 studies highlight the analysis of animals, apes, and primates for SFV surveillance and evolution inside the host.

2-Meta-Analysis:

Fifteen of the 30 studies that were a part of the systematic review measured seroprevalence in exposed workers without using a control group; as a result, they were left out of the subsequent analyses. Thus, 15 studies were included in the meta-analysis. Human population settings that are engaged in direct contact with pets, primates, and apes had an estimated cumulative odds ratio that was significantly higher than that of the controls (OR 1.93; 95% CI 1.15; 3.23) (Table 1 & Fig. 1).

Table 1: Meta-analysis of 12 studies of a human population exposed to SFV infection

S.No.	Study	OR	CI (Lower Limit)	CI (Upper Limit)	Weight
1.	Switzer et al., 2004	0.67	0.56	1.411	1.02%
2.	Murray et al., 2009	2.55	0.59	11.00	5.6%
3.	Khan et al., 2009	8.93	3.00	26.60	7.30%
4.	Huang et al., 2012	2.46	0.51	11.85	5.08%
5.	Soliven et al., 2013	0.78	0.03	17.93	1.89%
6.	Mouinga-Ondeme et al., 2013	1.67	0.11	25.26	2.60%
7.	Switzer et al., 2016	7.71	2.20	27.03	6.46%
8.	Materniak-Kornas et al., 2019	2.55	0.59	11.00	3.61%
9.	Shankar et al., 2020	1.00	0.10	10.52	3.38%
10	Hashimoto-Gotoh et al., 2020	2.03	0.80	5.16	8.18%
11	Materniak-Kornas et al., 2022	2.81	1.30	6.53	9.96%
12	Couteaudier et al., 2022	6.50	0.10	10.52	3.3%

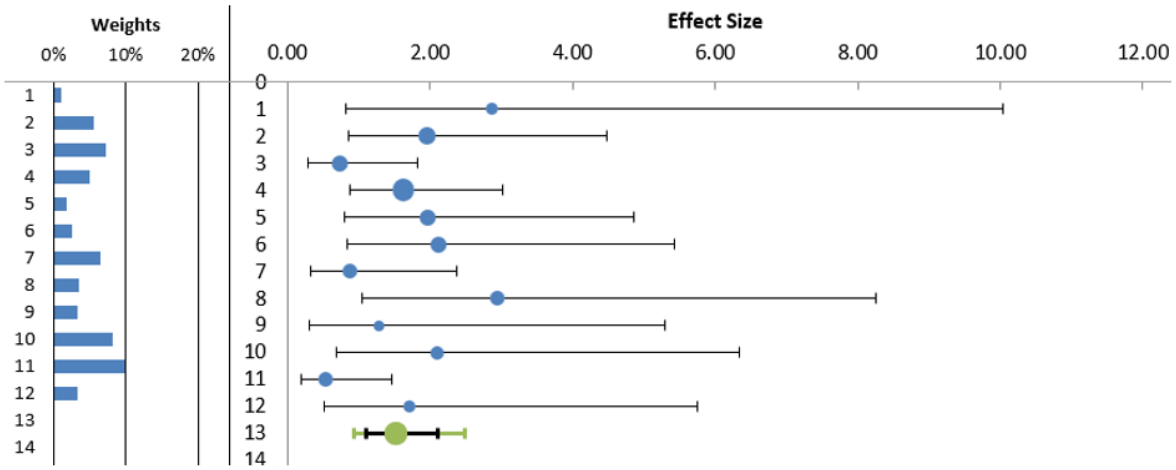

Fig. 1: Forest plot of odds ratio for SFV cases (diagnosed by antibodies) among exposed human population setting

The I^2 index revealed a moderate level of heterogeneity between the studies (51.27%). The funnel plot showed some evidence of publication bias (Fig. 2), mainly due to the absence of small negative studies. However, Egger's test was non-significant ($p = 0.938$). Then, we looked into whether the observed heterogeneity had anything to do with the time frame of the studies. In studies that were published up until 2013, we saw a significantly higher risk for the human population exposed to non-human primates, apes, and monkey caretakers (OR 1.83, 95% CI 0.33-1.05), whereas in more recent studies, the odds were no longer significant (OR 1.08, 95% CI 0.63-1.85) (Table 2 & Fig. 3). The plot is a powerful tool for summarizing and visualizing meta-analysis of multiple studies. The effectiveness of the hypothesis into consideration, intuitive comparison, and improved publication clarity are provided by such plots. The confidence interval provides the confidence intervals and summary estimates of the multiple studies.

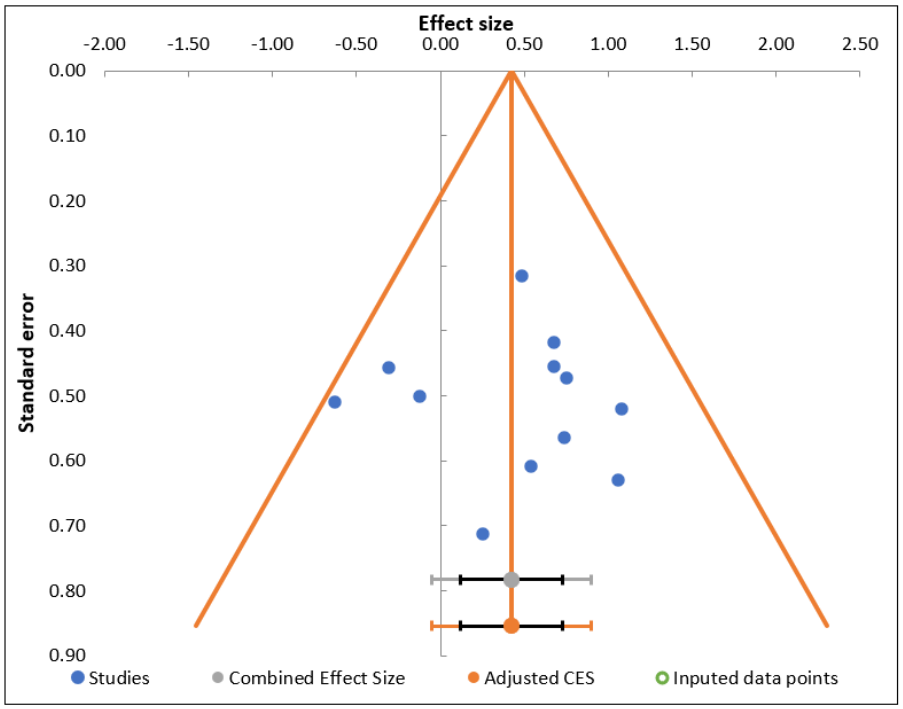

Fig. 2: Publication bias. Funnel plot of studies reporting SFV (diagnosed by antibodies) associated with human exposure.

Table 2: Subgroup comparative analysis of studies performed before and after 2013.

S.No.	Study	OR	CI (Lower Limit)	CI (Upper Limit)	Weight
1.	Switzer et al., 2004 [26]	2.88	0.82	10.03	8.25%
2.	Murray et al., 2009 [36]	1.96	0.86	4.49	16.89%
3.	Khan et al., 2009 [38]	0.73	0.30	1.82	14.60%
4.	Huang et al., 2012 [1]	1.63	0.87	3.02	26.12%
5.	Soliven et al., 2013 [39]	0.88	0.33	2.38	12.42%
6.	Mouinga-Ondeme et al., 2013 [34]	2.95	1.05	8.25	11.63%
	Until 2013	**1.83**	**0.705**	**4.99**	**89.91%**
7.	Switzer et al., 2016 [30]	1.96	0.79	2.55	10.08%
8.	Materniak-Kornas et al., 2019 [3]	2.13	0.83	4.85	8.25%
9.	Shankar et al., 2020 [14]	1.29	0.31	5.43	25.57%
10	Hashimoto-Gotoh et al., 2020 [6]	0.53	0.19	5.30	24.24%
11	Materniak-Kornas et al., 2022 [4]	1.71	0.08	1.47	12.44%
12	Couteaudier et al., 2022 [8]	0.48	0.10	2.31	21.56%
	After 2013	**1.35**	**0.38**	**3.651**	**102.14%**
	Combined effect size	**1.76**	**0.58**	**5.29**	

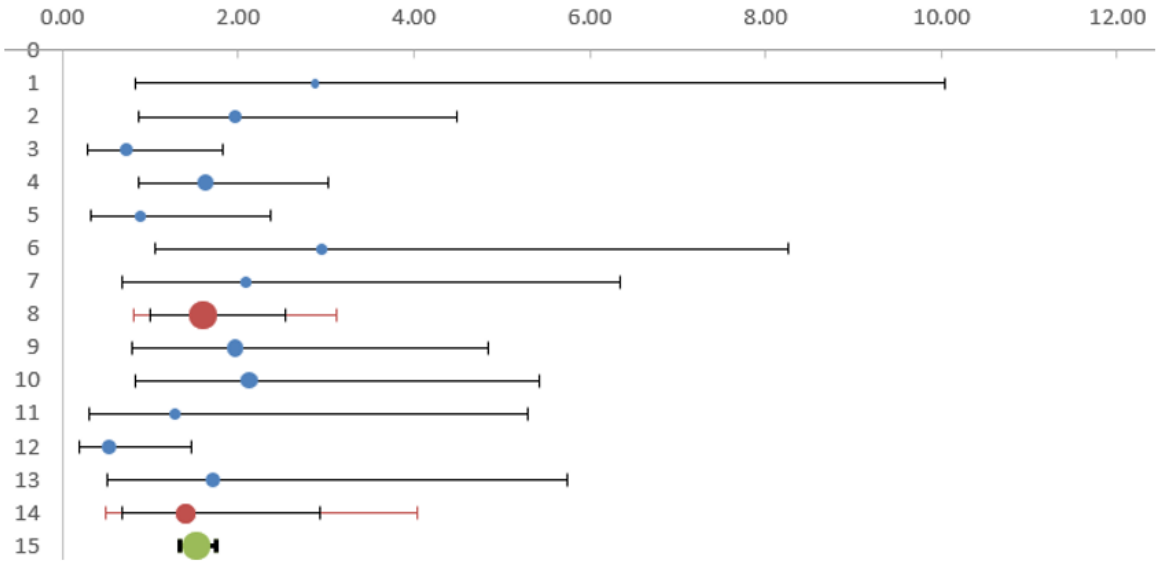

Fig. 3: Forest plot depicting comparative analysis of studies published before and after 2013.

DISCUSSION

This study confirmed that the Simian Foamy Virus (SFV) infection appears non-pathogenic in itself but it may increase the morbidity of other pathogens in co-infection. Foamy viruses (FV) are transmitted mainly through saliva but the possibility of the foamy virus undergoing mutation and recombination leads towards pathogenicity (Kehl *et al.*, 2013; Materniak-Kornas *et al.*, 1973). This decrease in pathogenicity, which now largely overlaps that of the general population, may have been caused by the increased awareness of SFV and the dissemination of prevention strategies (Schweizer *et al.*, 1997; Santos *et al.*, 2019). Advancing the knowledge of these simian foamy viruses requires a meta-analysis of research on foamy viruses. It can resolve discrepancies, elucidate transmission dynamics, and provide guidance for public health and treatment approaches by combining the available data. The results will eventually add to scientific understanding and useful applications in health and medicine by filling in existing study gaps and directing future studies (Shafiee *et al.*, 2023; Ganeshkumar *et al.*, 2018; Dallmeyer *et al.*, 2023; Achong and Mansell, 1971).

Our systematic review identified that the majority of viral pathogens that have emerged in humans have originated from

animal species. Simian foamy viruses (SFV) are retroviruses that are closely phylogenetically related to simian immunodeficiency viruses and simian T lymphotropic viruses are transmitted to humans via non-human primates (Murray and Linial, 2006; Gessain *et al.*, 2013; Meiering and Linial, 2001; Leendertz *et al.*, 2008). They are mainly activated in a non-pathogenic way and responsible for causing co-infection. (Leendertz *et al.*, 2008 and Liu *et al.* 2008) validated the interspecies transmission of simian foamy viruses in a natural predator-prey system. Molecular ecology and natural history of simian foamy virus infection in wild living chimpanzees reported the case of co-infection caused by non-primate humans (Switzer *et al.*, 2004). The acquisition of additional infections after SFVcpz infection seems to first occur via vertical transmission in adulthood, possibly as a result of combative interactions (Blasse *et al.*, 2013). As a matter of fact, rhesus macaques and human subjects in some South Asian nations share a geographical region that serves as the "home range" of both primate populations (Switzer *et al.*, 2016; Feeroz *et al.*, 2013; Jones-Engel *et al.*, 2008). Such frequent interactions may result in the transmission of viruses between different species. Additionally, SFV zoonotic infection has been found in South and Southeast Asian nations among various contexts of interspecies contact, such as "monkey temple" workers, pet owners, and people living near free-ranging macaques (Locatelli and Peeters, 2012). Each year, human-macaque commensalism occurs frequently in these regions' monkey temples, putting a huge number of people, including tourists, at risk for macaque bites. Furthermore, over the past century, there probably has been a significant increase in human-potentially infected NHP contacts in Central Africa, mostly between hunters and their spouses and butchers (Betsem *et al.*, 2011). This is thought to be because hunting activity has increased due to a combination of factors including urban demand for bush meat, easier access to NHP habitats made possible in part by logging roads, easier access to firearms, an increase in the number of people residing in forested areas, and the consequent rise in local food needs. Recently, women who were infected were also discovered in the Democratic Republic of the Congo (Mouinga-Ondémé *et al.*, 2012; Murray and Linial, 2006).

Following severe bites from mostly gorillas, a recent report from Gabon confirmed such frequent cross-species transmission in hunters. The presence of SFV in both captive and wild non-human primates and human populations is evaluated to better understand viral zoonosis. Samples were collected from hunters and non-human primate laboratory workers to show clear and extensive cross-species transmission of SFV (Murray and Linial, 2019). In several areas of the tropical forest, people who were hunting or playing with pets when they were severely bitten or scratched by non-human primates had antibodies against the SFV. The SFV strain isolated from a De Brazza monkey clustered with the sequence obtained from the person who had been bitten by an unidentified *Cercopithecus* genus. Over a period of 10 years, genetic variation to the virus following transmission to a human via severe bite is investigated inferring high nucleotide similarity through comparative sequence analysis (Gessain *et al.*, 2013).

Studies conducted in Simian Foamy Virus (SFV) are considered pathogenic when causes co-infection with human T-cell lymphotropic virus-1 (HTLV-1). Because the majority of humans do not have direct interactions with NHP, SFV zoonotic transmission is not very common. On the contrary, the development of SFV as gene therapy vectors for the treatment of human diseases is of great interest (Khan, 2009). Foamy viruses are retroviruses that can be used to express desired genes for a long time by permanently integrating into the genomes of cells. FV vectors are more likely to be chemically stable than vectors with RNA genomes, such as ortho-retroviruses, because the functional FV genome is DNA (Soliven *et al.*, 2013). These characteristics, along with the fact that they are not pathogenic, make

SFV promising candidates for the creation of viral vectors.

This study has some limitations too. The major limitation is the lack of sufficient cohort-based comparative studies targeting human and animal hosts highlighting the identification of antibodies and characterization in haematological settings. Another limitation is the lack of different experimental settings utilized to define serological positivity. Beyond these limitations, in this meta-analysis, we have included a detailed review of the studies that validate the cross-species transmission of SFVs among non-human primates and humans. The benefit of this study is that it gives public health authorities useful information about the efficacy of current measures for preventing SFV through its analysis of the most recent literature.

Conclusion

Many people are at risk for non-human primate bites and SFV transmission because of infectious disease risk factors. According to this review, meat hunters, zoo caretakers, and butchers are the most exposed groups, and risk has to be decreased by analyzing the results of preventive studies. The geographic exposure to SFV in working environments varies from population to population, particularly among butchers and caretakers. Therefore, initiatives should be taken to increase vulnerable worker's awareness of the spread of SFV. These could include joint efforts by neighborhood public health departments and labor/civil organizations to educate employees about the risks involved and the requirement to see a doctor after being bitten by a susceptible primate.

Declarations:

Ethical Approval: The study does not contain any humans and animal studies. It is only focused on a meta-analysis study.

Conflict of interests: All the authors read and approved the manuscript and declare that there is no conflict of interest.

Authors Contributions: All authors contributed equally, and have read and agreed to the published version of the manuscript.

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Availability of Data and Materials: The data presented in this study are available on request from the corresponding author.

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