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Monkeypox Virus Hosts and Transmission Pathways: A Systematic Review of a Zoonotic Pathogen

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May 2022

Acknowledgements

I have many people I would like to give credit to for not only guiding me in writing this thesis but who also inspired me to pursue the unknowns in science and push myself to rise to the challenges that come with doing honors research. First, I would like to thank Dr. Brent Newman. He worked as an active mentor to me throughout every step of the way of completing this paper. During the entirety of the time it took to write my thesis, he sat with me weekly and gave me very effective and specific advice that really helped me understand the scope of my work and how to best approach it to present to the scientific community. I owe him many thanks for his mentorship throughout writing my first scientific paper.

I would also like to give great thanks to Dr. Kristian Forbes, who has played a huge role in facilitating my place in the Forbes Research Lab. I appreciate his expertise in helping me choose this topic. His offering of expert advice greatly advanced this paper to where it is, and I owe him many thanks for the time and effort he used to help me get to that place. Thank you also to Sarah Chewning, our lab manager, for being so supportive throughout this process.

In addition, I'd like to acknowledge past professors I have had who have left me feeling inspired to complete research by energetically teaching me material I will need throughout my professional life. Specifically, I'd like to thank Dr. Kumar, Dr. Daniel Lessner, Dr. Naithani, Dr. Forbes, and many other professors who contributed to my education here at the university.

I would be far from finished if I didn't highly acknowledge my thesis defense committee. Thank you to Dr. Kristian Forbes, Dr. Kusum Naithani, Dr. Brenda Zies, and Dr. Johanna Marie Thomas for taking time out of their schedules to contribute their expertise to the defense of this thesis.

Finally, I'd like to thank my friends and family for supporting me and inspiring me not only throughout this thesis writing process but also through my undergraduate career. None of this could be done without their support, and I will be forever grateful for the places they all have in my life.

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Abstract

Monkeypox virus (MPXV) is an etiological agent of Monkeypox with origins believed to be of Central/West Africa. As a member of the orthopoxvirus family and due to its increasing emergence, it has become a pathogen in need of research. This paper works to find common trends of transmission routes and reservoir hosts in previous publications through a systematic review. Articles found on Web of Science containing the search term “Monkeypox” were sorted based on relevance to the review topics of potential reservoir hosts and transmission routes of Monkeypox virus. Through Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), 1,036 articles were evaluated, 905 were excluded, and 131 were included. Results showed the African Rope Squirrel, the Giant Gambian Rat, and various other squirrels (as a general category) were most likely to be considered as potential reservoir hosts for MPXV. Respectively, these species were mentioned in 26.80%, 19.59%, and 15.46% of the articles that recommended a potential reservoir host. Direct contact most often was reported as the probable transmission route for MPXV. Approximately 83.33% of articles that had a comment about transmission possibilities said direct contact causes spillover of MPXV from zoonotic hosts to humans. In conclusion, findings from the review give sufficient guidelines on where public health officials can take research to find clear answers on MPXV transmission.

Introduction

Monkeypox virus (MPXV) was first discovered in cynomolgus monkeys in a laboratory setting in Copenhagen, Denmark in 1958 (Ladnyj et.al. 1972). This discovery was the world's first introduction to this additional human orthopox virus, other than smallpox, causing public health researchers to question where and when MPXV might appear next. In 1970, the first human case was reported in the Basankusu territory of the Democratic Republic of the Congo in a nine-month-old child who presented with symptoms like smallpox, but later was identified as MPXV (Ladnyj et.al. 1972). This case would serve as an initial warning sign to public health officials that the virus had potential to increase in infection rate among humans.

Until 2003, MPXV cases were sporadically documented in Central and West Africa regions (Essbauer et.al. 2009). However, outbreaks began to occur in Sudan, the Democratic Republic of the Congo (DRC), and eventually, imported cases were documented in the United States in the early 2000s (Essbauer et.al. 2009). As MPXV cases reached a global scale, it became clear that humans were a highly susceptible host to MPXV infection. Further, reported outbreaks in countries such as Sudan, Cameroon, the DRC, and Nigeria started to become more frequent (Levine et.al. 2007; Sadeuh–Mba 2019) (Figure 1). During this time, researchers also identified two different MPXV strains; a Western strain and a Central strain, with the Western strain causing more severe illness in humans (Levine et.al. 2007). This was the first indication that MPXV had mutated and was evolving to become more infectious and thus alerted public health officials to the seriousness of this emerging zoonotic pathogen and the need for increased surveillance.

Research suggests MPXV is naturally maintained in rodent populations and to a lesser extent non-human primates (NHP), however, the true reservoir host for the virus is currently unknown (Essbauer et.al. 2010). In addition, research on MPXV transmission pathways is ongoing. Therefore, a more comprehensive understanding of the potential/suspected host(s) and transmission pathways for MPXV is needed so that public health officials can develop and implement intervention strategies to reduce risk of human infection.

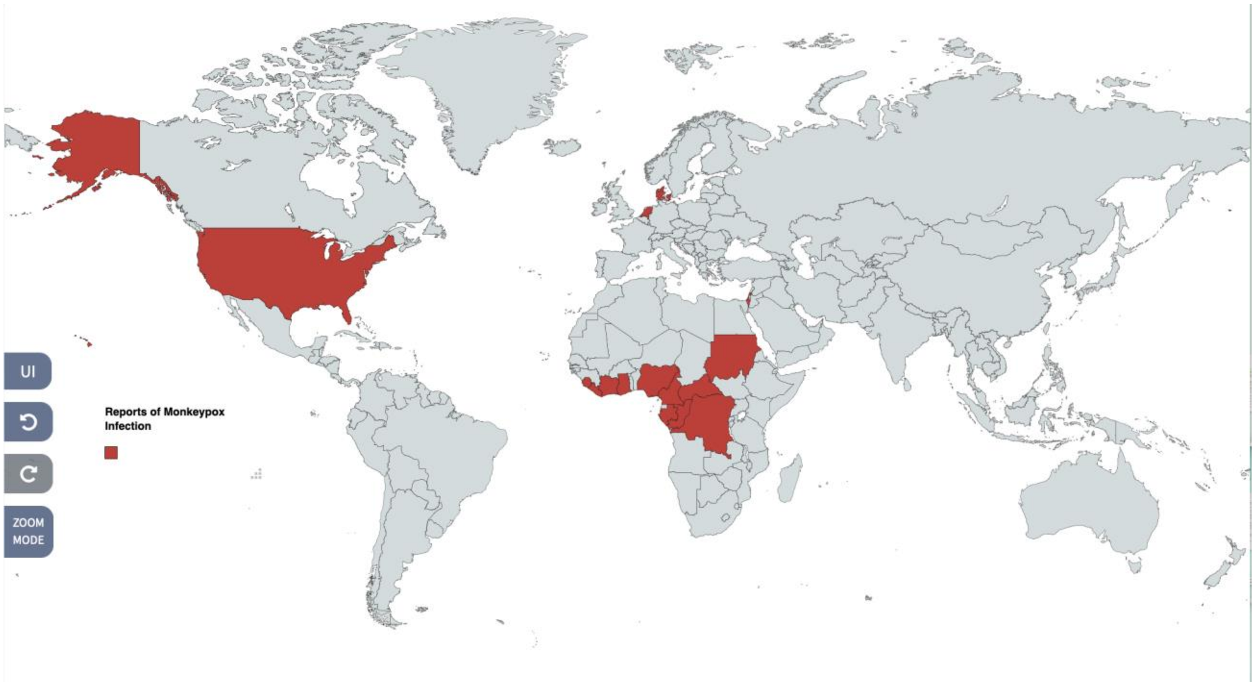

Figure 1. Geographic distribution of MPXV human cases with red indicating occurrence by country (Levine et.al. 2007; Sadeuh–Mba 2019; Ladnyj et.al. 1972; Essbauer et.al. 2009; Larkin 2003).

The purpose of this study is to systematically review and summarize what is currently known about MPXV animal hosts and primary transmission pathways. Published empirical data were used to identify reservoir host species and the mechanisms by which the virus has been transmitted amongst them. By sorting through over a thousand published articles on monkeypox virus and combining information into viewable data sets, this paper works to find areas worth conducting further research to better understand how humans can best protect themselves from contracting monkeypox virus by avoiding specific species known to host monkeypox virus as well as avoiding activities that enable virus transmission. PRISMA, the systematic review procedure, was used to guide the methods applied.

Methods

Protocol

PRISMA criteria were used to conduct data collection, analysis, and interpretation of source -information. PRISMA criteria were also used for this project to complete a truly systematic review of existing literature pertaining to possible monkeypox virus hosts and transmission routes (http://www.prisma-statement.org).

Search Strategy and Eligibility Criteria

A search was conducted using the keyword "monkeypox " via Web of Science database. Using this keyword enabled a thorough selection of articles. Publications were not restricted by year. Therefore, all published documents containing the word/topic "monkeypox" were returned. After completing the initial search, 1,036 articles were returned and exported to Microsoft Excel via Web of Science citation exporter. The articles were only retrieved via Web of Science, therefore, no duplicates needed to be removed.To ensure consistent return of results, this search was repeated three times. The same number of articles were returned each time, and after, it was certain that this search could be repeated in experimentation. Microsoft Excel was then utilized to organize article titles, DOI's, authors, year of publication and other pertinent information regarding the citations.

Study Selection

The first refinery step in narrowing down articles was done by reading through each title of the 1,036 articles retrieved and determining relevance to monkeypox virus transmission and/or possible host data. Excluded articles commonly had topics covering possible vaccinations, treatments, and clinical data of monkeypox virus occurrences. Other excluded articles discussed viruses related to monkeypox virus, however they did not fit inclusion criteria. Articles that passed the title screening criteria either discussed MPXV transmission pathways, possible hosts, or case studies. After title evaluation, 295 articles were identified and used in the PRISMA screening criteria, and 741 articles were excluded. Next, article eligibility was assessed via full review of abstracts, and article text. This resulted in 131 suitable articles and 164 that were considered unsuitable and therefore excluded based on inclusion/exclusion criteria. All suitable articles were then read to further assess and confirm inclusion.

Data Collection Process and Data Items

An independent format was utilized to collect data on the remaining 131 articles. A google sheet was made with a copy of the article's title, authors, DOI, and year of publication. Columns were added for data collection. These were titled as possible animal reservoirs, possible intermediate host, transmission route, region, and time. The respective categories stated were for collection of any mentions of each subject in each respective paper. Each individual article was read to identify pertinent information or discussion of monkeypox virus. Articles that referred to or provided information pertinent to animal hosts of monkeypox virus, transmission to humans, date of transmission/occurrence, or geographic location of occurrence were organized, and this information was recorded in google sheets.

Risk of bias in individual studies

When providing background information on MPXV reservoir hosts and transmission routes, it was found that many articles cited the same studies to support their research. These commonly cited articles were not considered more heavily than other articles, which ideally reduced any skewing of results.

Synthesis of Results

Data collected was transformed into viewable platforms via figures and table. These figures and tables make suggestions on potential reservoir hosts and transmission routes of MPXV by measuring number of mentions in the articles collected. First, a table was made compiling a list of sources for each suggested species named as potential reservoir hosts for monkeypox virus. A list of sources stating potential transmission routes was also compiled (i.e., bibliography). Graphs were then created based on the table. Conclusions presented herein were based on the number of times articles claimed an answer to the question of which species is likely to be a monkeypox virus reservoir host and which method is likely for transmission.

Summary measures, risk of bias across studies, and additional analyses are part of PRISMA criteria. However, these criteria were not applicable to this systematic review and therefore, were not included in this study.

Results

Study Selection

After searching the Web of Science for articles containing the keyword “monkeypox,” 1,036 articles were returned. Articles included ranged from case studies of monkeypox virus to reviews of monkeypox virus. No matter how general or how specific the given article was in its writing of monkeypox virus, if it mentioned possible hosts or transmission routes, they stayed included in the search methods.

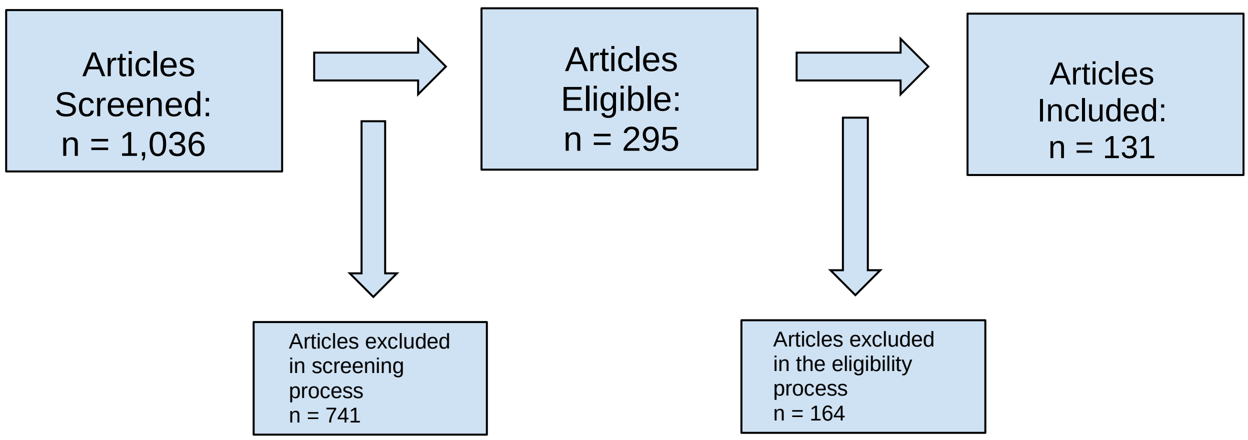

Figure 2. Pictorial display of literature assortment using the PRISMA criteria. Articles included in the review can be seen in the “included” box.

In the end, 131 articles made it through the eligibility process to be in the “included” category for this study. The figure above displays the organization of the study via a flow chart (Figure 2). From there, the 131 articles remaining were read again, and their mention of possible animal reservoirs, transmission routes, and regions of monkeypox virus occurrence were recorded via a Google sheet. These findings were then converted to a more condensed chart that lists the sources that claim certain animal hosts and transmission hosts of monkeypox virus.

Study Characteristics

Table 1. Demonstrates the proportions of articles that said specific species were potential reservoir hosts for MPXV. It also demonstrates said regions where it has occurred. The proportions mentioned in literature gives a percentage of articles out of those that mentioned a potential reservoir host that said it was due to a given species in the table.

Vertebrate Reservoir	**Region (if applicable)**	**Proportion Mentioned in Literature**
African Rope Squirrels (funisciurus sp.)	DRC, Basankusu Territory	26/97 = 26.80%
Squirrels	West Africa, DRC, Zaire	19/97 = 19.59%
Gambian Giant Rat	Africa and Midwest US (Wisconsin)	15/97 = 15.46%
Gambian Sun Squirrel (heliosciurus spp.)	DRC	7/97 = 7.22%
Sooty Mangabey (cercocebusatys)		5/97 = 5.15%
Dormice	Africa	5/97 = 5.15%
Prairie Dog	Indiana, Wisconsin	3/97 = 3.09%
“Bushmeat”		3/97 = 3.09%

Giant Anteater		2/97 = 2.06%
Giant Pouch Rat		2/97 = 2.06%
Thomas's Rope Squirrel (F. anerythrus)		2/97 = 2.06%
Hedge Hog	Africa	1/97 = 1.03%
Jerboa	Africa	1/97 = 1.03%
Opossum	Africa	1/97 = 1.03%
Woodchuck	Africa	1/97 = 1.03%
Antelope		1/97 = 1.03%
African Civet		1/97 = 1.03%
Cricetomys		1/97 = 1.03%
Graphiurus		1/97 = 1.03%

Table 1 describes specific species mentioned in articles kept in the included article category that have potential to be reservoir hosts for monkeypox virus. Some are very specifically named species, while others are more general families or genuses of a given vertebrate found in African

regions. While 131 articles were used total in this study, not all of them mentioned a specific possible reservoir host for MPXV.

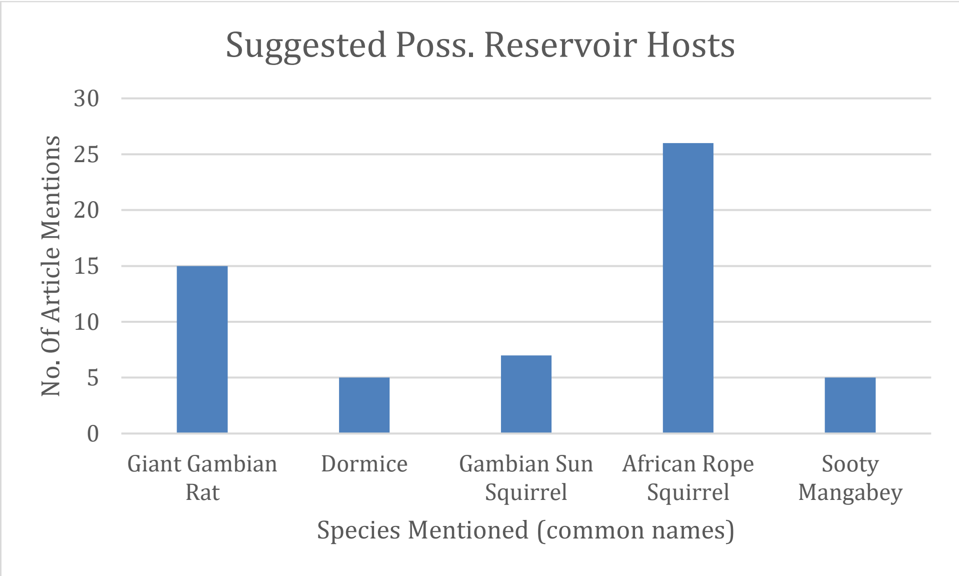

Figure 4. Results of *Table 1* in graph form. The x-axis represents the five most commonly mentioned potential reservoir hosts for MPXV, and the y-axis shows how many article "mentions" a given species received in the study.

In Figure 4, results of *Table 1* are recorded via a bar graph for viewing of species with majority of mentions in the literature included in the review (Figure 4). Other articles made mention of only a possible transmission route for MPXV, without identifying a host species, so those were not included in *Table 1*. Species are reported in order of likelihood to be a potential reservoir host for MPXV based on how often they were seen mentioned in the collection of articles extracted through PRISMA criteria. Regions in the world where they were mentioned to be known to host MPXV is also noted in the table as well.

Table 2. Proportion of articles that mentioned a potential transmission route for MPXV. Various transmission mechanisms are listed on the left, and the proportions of articles that recommended a specific transmission method are given in the right column.

Transmission Mechanism	**Proportion Mentioned in Literature**
Direct	110/132 = 83.33%
Aerosol	11/132 = 8.33%
Fomite	11/132 = 8.33%

Table 2 displays a summary of most mentioned transmission routes for MPXV. Direct transmission was most articles' suggestions for possible transmission routes for MPXV. Aerosol and fomite transmission were significantly mentioned as well for being possible ways MPXV can spillover from animals to humans.

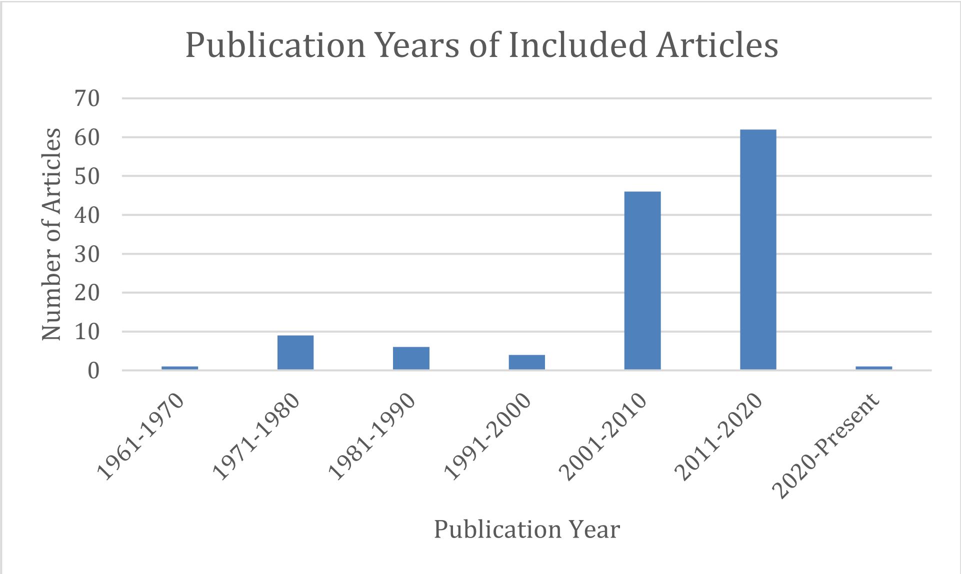

Figure 3. Trends of publication by years. The x-axis shows the progression of time since MPXV began to be researched by decade, and the y-axis shows the quantity of articles that were published in a given decade.

The figure above displays the trend of articles that discuss MPXV potential reservoir hosts and transmission methods (Figure 3). Peak article publication concerning MPXV can be seen in the early 2000s, where more spread was also observed as well. This figure was completed to show general relevance of MPXV to the world based on how many articles were being published in certain time periods.

Discussion

Overall, 131 articles were identified from Web of Science based on PRISMA search criteria. Although the true reservoir host(s) for MPXV is still currently unknown, evidence from this systematic review indicate that African rope squirrels, Gambian giant rats, and other species of squirrels are most likely the common carriers for this virus in the wild. In addition, direct transmission most often was claimed to be the dominate method of transmission for MPXV. Finally, it was found that research concerning MPXV transmission methods and potential reservoir hosts have quickly increased, indicating the rising popularity of MPXV research.

Across the board, it is recognized that MPXV was first recognized in NHP in Copenhagen, Denmark (Ladnyj et.al. 1972). As researchers progressed in their work, NHP were assumed as the species MPXV originated in due to the species being the first the virus was isolated in, however, taking the scope of viewing all literature ever published in Web of Science over the subject suggests otherwise (Essbauer et.al. 2010). Conclusions from this paper did support the idea that MPXV likely could originate from bushmeat. Bushmeat can be defined as food sources in the form of meat that have been hunted from wildlife sources (Monroe et.al. 2015). Support from the literature suggests this indeed is a likely opportunity for humans to be directly exposed to species (which include the suggested potential reservoir hosts) that naturally host MPXV (Reynolds et.al. 2019). Very few articles disagree on the potential ways MPXV spills over from animals to humans, however the conclusions reached in this paper contradict those common ideas that MPXV likely originated in NHP.

Research is greatly needed to find isolated viral material of MPXV. These suggestions taken from reading through most relevant literature could act as suggestions for future research over MPXV. However, literature mentions quite a few different possible reservoir hosts for MPXV (around 18 different possible species were mentioned in total), so the strength of this conclusion is not strong enough to make the claim that these species with majority of mentions in the reviewed literature are likely to concretely be named the reservoir host of MPXV. This review is a true suggestion of what or what could not be the truth about the reservoir host and transmission route for MPXV. Nothing can be confirmed or denied here, so field research is greatly needed to increase clarity on these topics.

In conclusion, African rope squirrels, Gambian giant rats, and other species of squirrels are likely to be a possible reservoir host for MPXV through direct transmission. Accumulation of this information via a literature review gives helpful suggestions for future research over the virus and could direct future research resources in a helpful direction.

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