Asian Journal of Research in Infectious Diseases

Volume 13, Issue 3, Page 28-36, 2023; Article no.AJRID.101074
ISSN: 2582-3221

Pathogens Enter Mosquito's Salivary Glands through the Existing Lesions in their Organs: A Potential Transmission Mechanism for Infectious Diseases

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Author's contribution

The sole author designed, analyzed, interpreted, and prepared the manuscript.

Article Information

DOI: 10.9734/AJRID/2023/v13i3269

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/101074

Opinion Article

Received: 01/05/2023
Accepted: 06/06/2023
Published: 10/06/2023

ABSTRACT

Whether pathogens in the ingested blood meal can enter the salivary glands of mosquitoes is a decisive factor in disease transmission. Unlike the known mosquito-borne pathogens (e.g. ZIKA, dengue, etc.), most human pathogens cannot enter the salivary glands of mosquitoes, and their survival time inside mosquito is usually short. Studies have reported that some mosquito species infected with certain mosquito-borne pathogens developed lesions in organs (e.g. holes in the midgut). Therefore, some of the pathogens which cannot enter the salivary glands of mosquitoes on their own (PWCESGMTO) may quickly enter using the existing lesions in the organs. This highly plausible issue has been neglected in research, and may involve the transmission of many infectious diseases. Since PWCESGMTOes can usually survive inside mosquitoes for only short period, successful transmission occurs only if mosquitoes bite a non-infected person before the ingested pathogens die. Therefore, the infected people should usually be in close proximity. The present paper discusses the neglected issue and the puzzling correlation between mosquitoes and three example diseases, and calls for urgent research into the issue.

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Keywords: Mosquito; infectious disease; transmission theory; salivary glands.

1. INTRODUCTION

Mosquitoes can carry viruses, bacteria, and parasites in their saliva, and can transmit the pathogens between humans through their saliva with subsequent bites. For this mode of transmission (known as biological transmission), the pathogens in an ingested blood meal must enter the salivary glands of mosquitoes. Only a small portion of pathogens can infect cells of mosquitoes and enter the salivary glands, such as, the mosquito-borne pathogen Zika, dengue, chikungunya, etc. Studies have shown that some mosquitoes infected with certain mosquito-borne pathogens developed lesions (e.g., holes) in the midgut. Therefore, for pathogens which cannot enter the salivary glands of mosquitoes on their own (PWCESGMTO), some may use these lesions in mosquito's organs as portals to enter the salivary glands. In the present paper, we discuss this neglected issue and the puzzling correlation between mosquitoes and three example diseases, and calls for further research into the issue.

2. INFECTIOUS DISEASES AMONG GAY AND BISEXUAL MEN

Gay and bisexual men have disproportionately high prevalence of HIV, syphilis, mpox (the new name for monkeypox), and some other infectious diseases. For example, they accounted for 89% of Mpox cases with sexual orientation reported outside sub-Sahara Africa (SSA) in 2022 [1], 66% of new HIV infections in the United States in 2019 [2], 70–84% of HIV cases in Australia and New Zealand between 1986 and 1994 [3], 83% of primary and secondary syphilis cases in the United States in 2014 [4], and 58% of total syphilis cases in Western and Central European countries [5]. These data suggest three possibilities: they have immune problems, they have unique behaviors that increase the risk, or they possess a distinctive factor that attracts certain insect vectors to transmit the diseases.

To date, no data have demonstrated the first possibility. Sexual contact between gay and bisexual men is recognized as a high risk factor (the second possibility). However, the question is that, the basic epidemiological characteristics of the three diseases are difficult to explain. For example, why do women and heterosexual men in SSA also have a striking prevalence of the three diseases, and why is the incidence of the three diseases several to more than ten times higher in the warm south of the United States than in the north [6–8].

Currently, mosquitoes and other insect vectors are not considered to be risk factors for these diseases (the third possibility). No data have shown that the three pathogens can enter the salivary glands of mosquitoes. However, as shown below, the mosquito transmission theory can easily explain the characteristics of the three diseases.

3. GEOGRAPHIC FACTORS

The United States is an ideal location to study infectious diseases, because of its large land area, large population, and large amount of research data. Figs. 1a–1c show that the prevalence of HIV, syphilis, and Mpox in states that border oceans or the Great Lakes was consistently several to more than ten times higher than that in the non-coastal regions (Central, Midwestern, and some Northern states) [6–8].

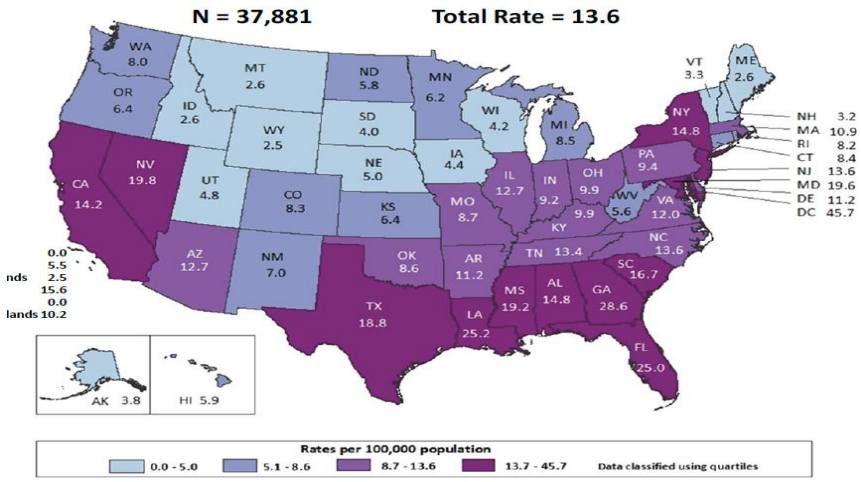
SSA accounts for 70% of global new HIV infections [9]. The prevalence of syphilis in SSA is almost 10 times higher than that in the rest of the world [10]. Mpox has been endemic to Western Africa for decades, with previous outbreaks rarely occurring outside Africa.

Above observations in the United States and SSA strongly suggest that certain geographic factors may play critical roles in the transmission of the three diseases.

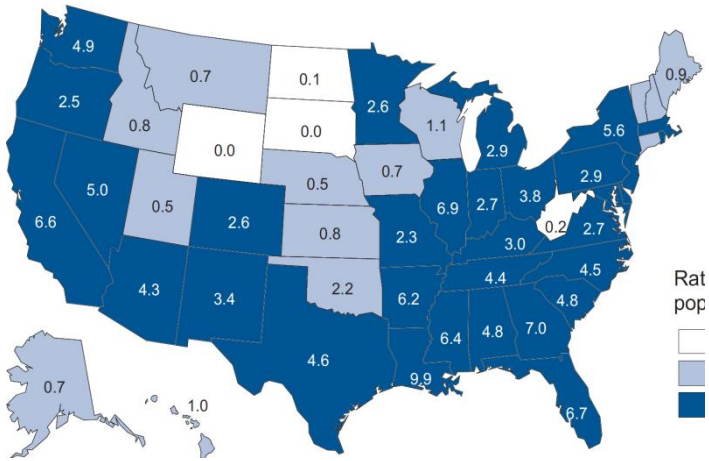
4. WARM WEATHER

In the United States, HIV, mpox and syphilis prevalence was much higher in the warm south than in the north (Figs. 1a–1c). Correlating with the disproportionately high prevalence of HIV and syphilis in SSA, the weather in most parts of SSA is warm throughout the year.

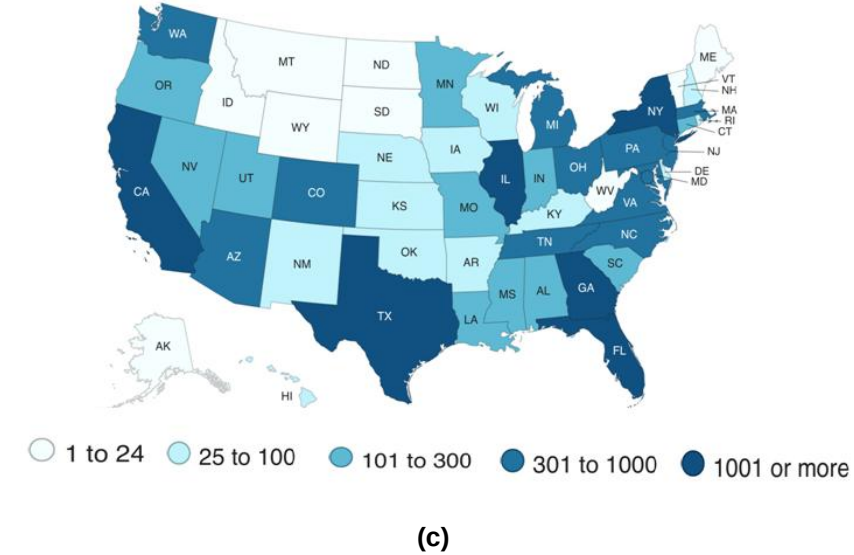
In regions that have both warm and cold seasons over the year, syphilis is a seasonal disease, with an incidence peaking in summer and early fall [11]. To date, three mpox outbreaks involving a group of cases outside Africa have all occurred during warm season.


N = 37,881
Total Rate = 13.6
Rates per 100,000 population
0.0 - 5.0
5.1 - 8.6
8.7 - 13.6
13.7 - 45.7
Data classified using quartiles

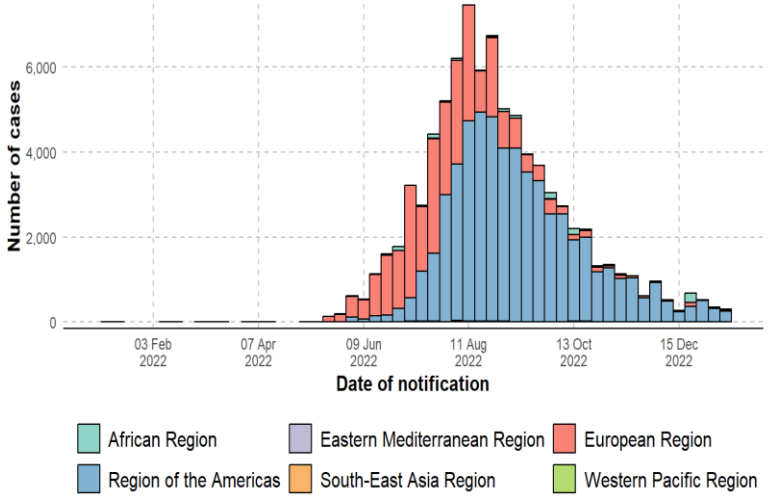
(a)



(b)


1 to 24
25 to 100
101 to 300
301 to 1000
1001 or more

(c)


Number of cases
Date of notification
African Region
Eastern Mediterranean Region
European Region
Region of the Americas
South-East Asia Region
Western Pacific Region

(d)

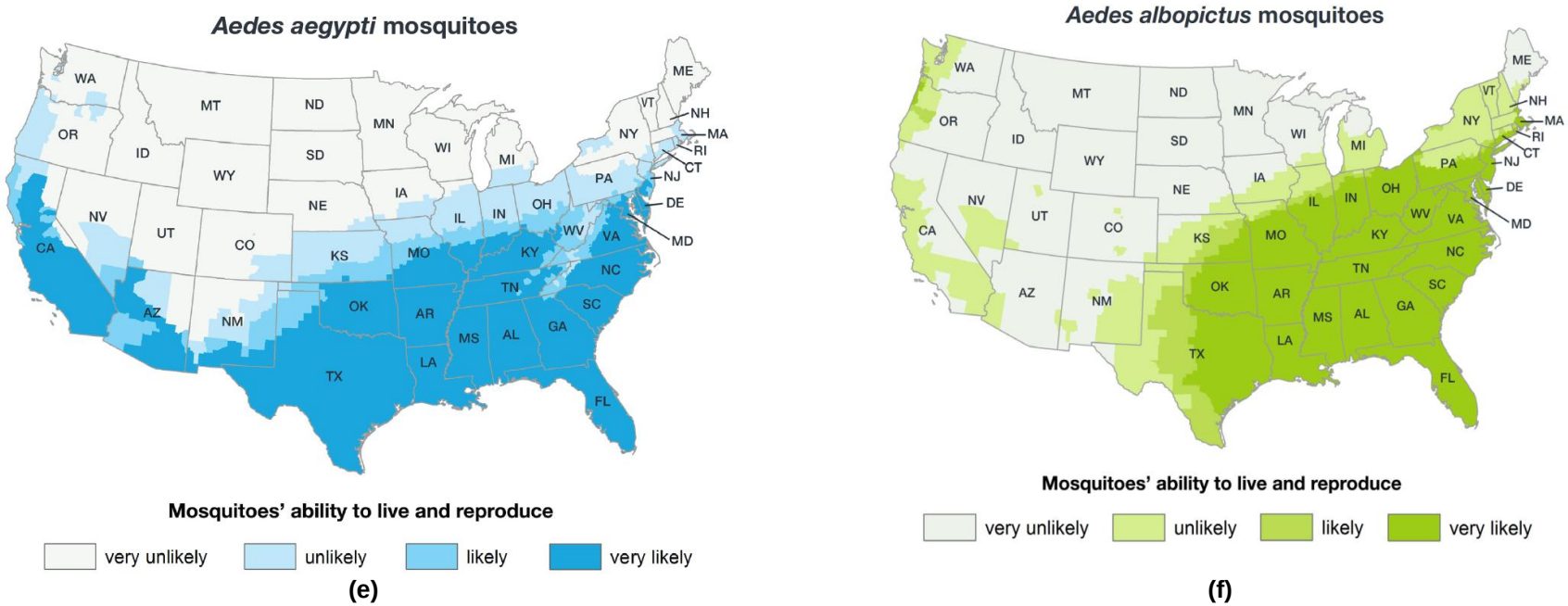


Fig. 1. (a) Rates of diagnoses of HIV infection among adults and adolescents per 100,000 population, United States, 2018. Source: CDC [6]. (b) Rate of primary and secondary syphilis per 100,000 population, United States, 2011. Source: U.S. Department of Health and Human Services, et al. [7]. (c) Mpox cases per 100,000 persons in the population at increased risk of mpox virus exposure, United States. Data as of October 21, 2022. Source: CDC [8]. (d) Global trend: epidemic curve shown for 2022 mpox outbreak. Source: WHO [14]. (e) Estimated range of *Aedes aegypti* in the United States, 2017. Source: CDC [15]. (f) Estimated range of *Aedes Albopictus* in the United States, 2017. Source: CDC [15]

The first outbreak of 71 cases was reported in the United States between May 15 and June 20, 2003 [12]. The second outbreak with several cases occurred in the United Kingdom in September 2018 [13]. The third was the 2022 outbreak, which ravaged Europe and America in the summer of 2022 (Fig. 1d) [14].

5. CORRELATION BETWEEN DATA OF MOSQUITOES AND THE DISEASES

In the United States, the estimated incidence of mosquito *Aedes aegypti* (Fig. 1e) and *Aedes Albopictus* (Fig. 1f) in regions that border oceans or the Great Lakes were consistently much higher than in non-coastal regions, in the warm south than in the north [15]. These data correlated the distribution of the three diseases in the United States (Figs. 1a–c). In 2020, 95% of global cases of malaria, a mosquito-transmitted disease, occurred in SSA, indicating that mosquitoes in SSA is very abundant and special. These data were consistent with the observations that women and heterosexual men in SSA also have a high prevalence of the three diseases, in contrast to the much lower rate outside SSA.

Mosquitoes are abundant in warm conditions. For example, the abundance of many mosquito species in Canada peaked in July, followed by August, September, and June [16]. These observations were correlated with the data that all the three mpox outbreaks outside Africa occurred in the warm season, and global syphilis infections peak in summer and early fall, and the prevalence of the three diseases are much higher in warmer than in colder regions.

The mosquito transmission theory can not only explain the geographic distribution of the diseases and their seasonal changes, but also epidemiological characteristics in other aspects. For example, homeless people are more likely to be exposed to mosquitoes. This fact is consistent with the observation that HIV and syphilis prevalence in homeless people is much higher than in the general population [17,18]. In SSA, girls need to stay home to take care of infected family members, and therefore, are exposed to the abundant mosquitoes to transmit HIV from the infected patients. This observation correlates with the striking data that girls in SSA have a much higher prevalence of HIV than boys.

6. NEGLECTED RESEARCH

For the biological transmission of diseases by mosquitoes, the pathogens must be able to infect the cells of mosquitoes, overcome multiple barriers (e.g. the midgut infection barrier, midgut escape barrier, salivary gland infection barrier, and salivary gland escape barrier) to enter the salivary glands, and avoid destruction by mosquito's immune system [19,20]. Unlike the mosquito-borne pathogens, the majority of pathogens that can infect humans do not have these abilities, and their survival time in mosquitoes is usually short (e.g., HIV, 48 hours).

Studies found that some mosquitoes infected with certain mosquito-borne pathogens in certain stages developed various lesions in midguts, such as holes in the midgut, loss of the brush border of the midgut, and detachment of cells from the epithelium [21–24]. Lesions may similarly occur in other organs. Studies has shown that apoptosis and other cytopathologic changes occurred more frequently in the salivary glands of mosquitoes infected with some mosquito-borne pathogens compared with uninfected controls [25,26]. According to common sense, a liquid can rapidly penetrate small holes and fissures. Therefore, some PWCESGMTOs in the ingested blood meal may use these lesions in organs to quickly diffuse into the salivary glands. Unfortunately, this issue has been neglected in research.

Studies reported that some mosquito-borne pathogens caused puncture holes in mosquito' midgut, and enhanced dissemination of other mosquito-borne pathogens through the puncture holes [27]. Therefore, some PWCESGMTOs in the ingested blood meal may pass through the holes in a similar manner. A recent study reported that microfilariae enhanced the transmission of other mosquito-borne pathogens by adhering to or otherwise associating with microfilariae [28]. This observation provides another potential means by which some PWCESGMTOs can enter the salivary glands.

For ingested pathogens that survive inside mosquitoes for only short periods, successful transmission occurs only if mosquitoes bite a non-infected person before the pathogen dies. Therefore, proximity between an infected and a non-infected person is important. The shorter the proximity (e.g., sleeping on a bed, or living in a house), the easier is the transmission. Therefore, people infected with this kinds of pathogens transmitted by mosquitoes should usually be in close contact.

People infected with HIV, mpox, or syphilis are usually in close contact. In contrast, people

infected with the known mosquito-borne diseases (e.g., malaria, ZIKA, or dengue, etc.) are anybody, regardless whether they are in close contact. This difference is often claimed as a reason for mosquitoes not being a risk factor for HIV, mpox, syphilis, or some other diseases. However, the mosquito-borne pathogens can infect the mosquitoes and survive inside mosquitoes for a longer period. Therefore, the infected mosquitoes can bite a person at any time to cause a transmission. In other words, the infected individuals are anybody, no matter near or far. Therefore, mosquitoes may transmit two types of diseases, one between people in close proximity, and the other between people regardless the proximity.

Mosquitoes often prefer to bite some people over others. Studies have reported that men are more likely to be attacked by mosquitoes than women, and mosquitoes prefer to bite certain people because of their body odor [29,30]. No study has been conducted on gay or bisexual men in this context.

7. PREVENTION PRACTICES

The result of the practice is a direct test of a theory. Isolation of infected individuals is an effective method for controlling mpoxes. This supports the close contact theory. However, this result also supports the mosquito transmission theory on diseases which spread between people in close proximity.

Progress in HIV prevention among adults has been limited. Historical success was surprisingly achieved in Uganda in the 1990s. Controversy remains regarding how success was achieved. Initial advice from the Uganda government was “faithfulness to one partner” [31]. This observation supported the sexual contact theory. However, the observation also supports the mosquito transmission theory; because people with fewer sexual partners mean less sleeping with others on a bed and less exposure to mosquitoes to transmit HIV from infected partners. After the incidence reduction, condom use was later implemented [31]. If condom use contributed to the further reduction in HIV infections, the result would support the sexual contact theory but not the mosquito transmission theory.

8. DISCUSSION

Mosquito is not recognized as a vector for HIV, mpox, syphilis, and many other diseases, largely because, these pathogens cannot enter the salivary glands, and their survival time inside mosquitoes is short. The present paper showed a close correlation between a broad range of the three diseases data and mosquitoes. Moreover, an important relevant scenario has been neglected in the research: there are existing lesions in organs of mosquitoes sometime due to pathological factors. These suggest that further research is still required to determine whether mosquitoes are a vector for HIV, mpox, syphilis, and some other diseases.

Since a liquid can rapidly penetrate small holes and fissures, and that, some mosquito-borne pathogens do use the existing holes in organs of mosquitoes to enhance their dissemination, it is plausible to hypothesize that, some of PWCESGMTOs in the ingested blood meal may use the existing lesions in organs of mosquitoes to enter the salivary glands. If so, mosquitoes may transmit many more diseases than previously recognized. A mistake in this issue could be fatal, and focused research is urgently needed to examine this issue. Here, I propose two experiments for global researchers. Since studies found that some mosquitoes infected with certain mosquito-borne pathogens developed lesions in organs, I propose allowing these mosquito species infected with the respective pathogens to be fed on blood containing PWCESGMIOs, and examine whether certain PWCESGMIOs appear in the salivary glands.

The second proposed experiment examines whether gay and bisexual men attract more certain species of mosquitoes than women and heterosexual men.

It is often stated that no evidence indicates that mosquito is a risk factor for HIV, mpox, or some other diseases. However, what evidence indicates that close or sexual contact is a risk factor for the diseases? Let’s discuss mpox as an example. Although the data that people infected with mpox are usually in close contact is claimed as the evidence supporting close or sexual contact being the risk factor, the problem is, this kind of data also supports mosquito is a risk factor. Importantly, epidemiological data for mpox is consistent with the mosquito transmission theory, and the close/sexual contact theory is difficult to explain why geographic distribution of mosquitoes overlaps that of mpox, and why the risk of close/sexual contact is much lower in cold season than in warm season, among women and heterosexual men than among gay and bisexual men. In 2022 outbreak, the prevalence of mpox

in US coastal regions with high prevalence of mosquitoes was consistently several to more than 10 times higher than in non-coastal regions (Fig. 1c). Consistent with the observation in the United States, all of the global top 10 infected regions in 2022 outbreak (the United States, the United Kingdom, Spain, France, Brazil, Germany, Peru, Canada, Mexico, and Colombia) [1] have a long boundary line surrounding oceans. Based on the close/sexual contact theory, spring and summer gatherings were claimed to be the reason for the rapid increase in mpox cases [32,33]. However, autumn is also a season for gatherings. Along with decreasing temperature from August to November during 2022, the daily cases of mpox decreased rapidly in countries in Europe and North America [34]. In contrast, during the same period in countries in warm Central/South America and Africa, the other three most infected regions in 2022 outbreaks, the daily cases did not decrease, or decreased much slower than in Europe and North America [34].

9. CONCLUSION

Some PWCESGMTOs may enter the salivary glands of mosquitoes using the existing lesions in organs, or via other means, and this potential mechanism may involve many infectious diseases. Mosquitoes may transmit two types of diseases, one between people in close contact, and the other between people regardless the proximity. Gay and bisexual men may possess certain distinctive factors (e.g. body odor) that attract some species of mosquitoes. Further research is warranted.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. WHO. Multi-country outbreak of monkeypox. External Situation Report 7. 5 October 2022.
   Available:https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--7---5-october-2022
   Accessed 19 April 2023.
2. CDC. Estimated HIV Incidence and Prevalence in the United States, 2015–2019. HIV Surveillance Report. 2021; Volume 26, Number 2.
   Available:https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-26-1.pdf
   Accessed 19 April 2023.
3. National Centre in HIV Epidemiology and Clinical Research. Australian HIV Surveillance Report. 1995;11(2).
4. CDC. Sexually Transmitted Diseases.
   Available:https://www.cdc.gov/msmhealth/STD.htm
   Last reviewed: September 16, 2022. Accessed 19 April 2023.
5. Kojima N, Klausner JD. An Update on the Global Epidemiology of Syphilis. Curr. Epidemiol. Rep. 2018;5(1):24–38.
   DOI: 10.1007/s40471-018-0138-z.
6. CDC. Diagnoses of HIV Infection in the United States and Dependent Areas, 2018.
   Available:https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2018-updated-vol-31.pdf Accessed 19 April 2023.
7. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Division of STD Prevention. Sexually Transmitted Disease Surveillance; 2011.
   Available:https://www.cdc.gov/std/stats/archive/Surv2011.pdf Accessed 19 April 2023.
8. CDC. Multi-National Monkeypox Outbreak, 2022 Report 4, United States; 2022.
   Available:https://www.cdc.gov/poxvirus/monkeypox/cases-data/technical-report/report-4.html
   Accessed 19 April 2023.
9. UNAIDS. Annual Report; 2009.
   Available:https://files.unaids.org/en/media/unaids/contentassets/dataimport/pub/report/2010/2009_annual_report_en.pdf
   Accessed 19 April 2023.
10. Newman L, Rowley J, Hoorn SV, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. Plos One, 2015;10:e0143304.
    DOI: 10.1371/journal.pone.0143304.
11. de Souza JM, Giuffrida R, Ramos APM, Morceli G, Coelho CH, Rodrigues MVR. Mother-to-child transmission and gestational syphilis: Spatial-temporal

epidemiology and demographics in a Brazilian region. Plos Negl. Trop. Dis. 2019; 13(2):e0007122.
DOI: 10.1371/journal.pntd.0007122.

12. Cunha BE. Monkeypox in the United States: an occupational health look at the first cases. AAOHN. J. 2004;52(4): 164–168.
13. Vaughan A, Aarons E, Astbury J, et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. Emerging Infectious Diseases 2020;26(4):782–5.
DOI: 10.3201/eid2604.191164.
14. WHO. 2022 Mpox (Monkeypox) Outbreak: Global Trends; 2022.
Available:https://worldhealthorg.shinyapps.io/mpx_global/ Accessed 19 April 2023.
15. CDC, Estimated range of Aedes aegypti and Aedes albopictus in the United States, 2017.
Available:https://stacks.cdc.gov/view/cdc/48315 Accessed 19 April 2023.
16. Shahhosseini N, Wong G, Frederick C, Kobinger GP. Mosquito Species Composition and Abundance in Quebec, Eastern Canada. J Medical Entomology 2020:57(4):1025–31.
DOI: 10.1093/jme/tjaa020.
17. National Coalition for the Homeless, HIV/AIDS and Homelessness. 2009.
Available:http://www.nationalhomeless.org/factsheets/hiv.html Accessed19 April 2023.
18. Ahmad-Abakur EH, Ahmed HAK, Abrahim-holi MA. Syphilis and Associated Risk Factors among Homeless in Khartoum State. Journal of Health Science 2018; 3(2):21–4.
DOI:10.5923/j.health.20130302.03.
19. Franz AWE, Kantor AM, Passarelli Al, Clem RJ. Tissue Barriers to Arbovirus Infection in Mosquitoes. Viruses. 2015; 7(7):3741–67.
DOI: 10.3390/v7072795.
20. Lee WS, Webster JA, Madzokere ET, Stephenson EB, Herrero LJ. Mosquito antiviral defense mechanisms: A delicate balance between innate immunity and persistent viral infection. Parasit Vectors. 2019;12(1):165.
DOI: 10.1186/s13071-019-3433-8
21. Santos JN, Lanfredi RM, Pimenta PFP. The invasion of the midgut of the mosquito Culex (Culex) quinquefasciatus Say, 1823 by the helminth Litomosoides chagasfilhoi Moraes Neto, Lanfredi and De Souza, 1997. Journal of Invertebrate Pathology. 2006;93(1):1–10.
DOI: 10.1016/j.jip.2006.05.002.
22. Weaver SC, Scott TW, Lorenze LH, Lerdthusnee K, Romoser WS. Togavirus-associated pathologic changes in the midgut of a natural mosquito vector. J. Virol. 1988;62(6):2083–2090.
DOI: 10.1128/JVI.62.6.2083-2090.
23. Trisnadi N, Barillas-Mury C. Live in Vivo Imaging of Plasmodium Invasion of the Mosquito Midgut. mSphere 2020; 5(5):e00692-20.
DOI: 10.1128/mSphere.00692-20.
24. Weaver SC, Lorenz LH, Scott TW. Pathologic changes in the midgut of Culex tarsalis following infection with Western equine encephalomyelitis virus. Am. J. Trop. Med. Hyg. 1992;47(5): 691–701.
DOI: 10.4269/ajtmh.1992.47.691
25. Girard YA, Schneider BS, EcGee CE, et al. Salivary gland morphology and virus transmission during long-term cytopathologic West Nile virus infection in Culex mosquitoes. Am J Trop Med Hyg. 2007;76(1):118–28.
26. Kelly EM, Moon DC, Bowers DF. Apoptosis in mosquito salivary glands: Sindbis virus-associated and tissue homeostasis. J Gen Virol. 2012;93(Pt 11):2419–2424.
DOI: 10.1099/vir.0.042846-0
27. Zytoon EM, El-Belbasi HI, Matsumura T. Mechanism of Increased Dissemination of Chikungunya Virus in *Aedes albopictus* Mosquitoes Concurrently Ingesting Microfilariae of Dirofilaria Immitis. Am. J. Trop. Med. Hyg. 1993;49(2): 201–7.
28. Vaughan JA, Turell MJ. Brugia malayi microfilariae transport alphaviruses across the mosquito midgut. Plos One. 2017; 12(2):e0172309.
DOI:10.1371/journal.pone.0172309.
29. Herre M, Goldman OV, Lu TC, Caballero-Vidal G, Qi Y, Gilbert ZN, et al., Non-canonical odor coding in the mosquito. Cell 2022; 185:3104–3123.
DOI: 10.1016/j.cell.2022.07.024.
30. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. Ann. Intern. Med. 1998;128:931-940.
DOI:10.7326/0003-4819-128-11-199806010-00013.

31. Stoneburner R, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. Science. 2004; 304(5671):714–718.
DOI:10.1126/science.1093166

32. WHO. Public health advice for gatherings during the current monkeypox outbreak
Available:https://www.who.int/publications/i/item/WHO-MPX-Gatherings-2022.1
Accessed 3 June 2023.

33. CDC. Mpox and Spring and Summer Events.
Available:https://www.cdc.gov/poxvirus/mpox/your-health/summer-events.html
Accessed 3 June 2023.

34. WHO. 2022-23 Mpox (Monkeypox) Outbreak: Global Trends. 3.2.9. Epidemiology curve by country.
Available:https://worldhealthorg.shinyapps.io/mpx_global/
Accessed 3 June 2023.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/101074