International Journal on Emerging Technologies 14(1): 42-51(2023)

ISSN No. (Print): 0975-8364
ISSN No. (Online): 2249-3255

A General Review of Sexually Transmitted Diseases (STDs) in Theoretical and Mathematical Modeling Aspects

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(Received 26 March 2023, Revised 21 April 2023, Accepted 22 May 2023)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: The present article gives a general overview of sexually transmitted diseases (STDs). There are several diseases that can often transmit through sexual routes. Some other routes are also responsible for the spread of the infections. According to the Centers for Disease Control and Prevention (CDC), some most common STDs having a very high impact on developing and developed countries are AIDS (acquired immunodeficiency syndrome); Hepatitis B; HPV (Human Papillomavirus infection); Candidiasis; Syphilis; Genital Herpes; Chlamydia; Gonorrhea; Trichomoniasis. Therefore, in this article, we discuss these STDs from theoretical as well as mathematical points of view. We found some shortages and some important ideas for the mathematical modeling of these STDs.

Keywords: HIV, AIDS, STDs, AVERT, Mathematical modeling.

I. INTRODUCTION

Sexually transmitted diseases also known as sexually transmitted infections or venereal diseases are very hazardous to the population around the world [5, 13-15, 17, 69, 70, 116]. There are several types of STIs that can be caused by bacteria, parasites, fungus, or viruses [14]. Widely recognized and influential STDs are AIDS (Acquired Human Immunodeficiency Syndrome); Hepatitis B; HPV (Human Papilloma Virus); Candidiasis; Syphilis; Genital Herpes; Chlamydia; Gonorrhea; Trichomoniasis all these will be discussed in the further sections [15]. STDs *viz*., HIV/AIDS, Genital herpes, Hepatitis B, and Human papillomavirus infection are viral diseases while Chlamydia, Gonorrhea, and Syphilis are bacterial diseases [13]. Candidiasis is a fungal infection while Trichomoniasis is parasitic. All the STDs discussed above are commonly spread by sexual intercourse, especially vaginal, anal, and oral sex [14, 17]. Some other routes are also responsible for the transmission of infections, e.g., blood transfusion, injecting drug use (IDUs), during childbirth, exchange of contaminated syringes and needles, traveling of the infected person across the country, exchanging sex toys, etc. [9, 10, 20]. Community transmission *viz.,* MSM (Male having sex with male), FSW (Female sex workers) also occur in several countries which are responsible for the spread of the infections [13, 15, 20].

According to the fact sheet provided by WHO, more than 1 million sexually transmitted infections are acquired per day globally and an estimated 376 million new infections from the diseases, chlamydia, gonorrhea, syphilis, and trichomoniasis occur each year [6]. It is not necessary that all the STDs have shown their symptoms. Some of them are symptomatic while others may be asymptomatic. Symptomatic STDs include HIV/AIDS, Human papillomavirus, Candidiasis, etc. while asymptomatic STDs include Hepatitis B, Gonorrhea, Trichomoniasis, etc. Some common symptoms shown by the STDs are headache, painless sores on the penis or vagina, illness weight loss, itching or burning during urination, etc. If a person has any one STDs, then it is more likely to get infected with others. Co-infection leads to a panic situation and

may cause very severe problems for the people like cancers, blindness, infertility, pelvic inflammatory disease (PID), etc. [5, 9, 10, 13, 14, 19]. Several efforts have been made by researchers and practitioners to control the infections. For some STDs, treatment is available while for others vaccination is given to reduce the impact [12, 16-18, 114]. Bacterial STDs (chlamydia, gonorrhea, and syphilis) and parasitic STD (trichomoniasis) are curable with antibiotics. The most effective medications for Herpes and HIV are antivirals that control the disease though they can't able to cure. Antiviral medications can help to fight the virus and slow down the damage of the liver against hepatitis B infection [17]. Some basic control strategies such as mutual monogamy, reducing the number of sexual partners, condom use during sex, routine medical checkup, counseling, sex education, avoiding contact with body fluids, and abstinence can be used to prevent people of getting infected [17-19].

Mathematical modeling of STIs is also in trends for several years which plays a crucial role to describe the behavior in terms of spread and rate of transmission which are helpful to minimize outbreak of the diseases [1, 2, 5, 6, 8, 10, 11, 72]. Several mathematical models to

STIs are developed by the researchers, made fruitful suggestions and shown that combinations of vaccination, treatment, isolation and quarantine are necessary to eliminate most infectious diseases [1-3, 7, 12]. It also useful in planning and evaluation of interventions particularly when controlled trial is impossible. Although policy decisions for public health would evaluate the measure effect directly at small scale but at large scale mathematical modeling help us [4, 7, 11]. Many situations where measuring of health outcome of interest is challenging or costly, modeling handle the situation [4, 6-8]. How much amount of vaccine or treatment is given to infected one under a fix budget is calculated through the modeling. There is no correct model in transmission dynamics of diseases, different types of models are applicable for the same disease which depends upon time frame of work, available data and the question being addressed for the same.

II. MATERIALS AND METHODS

A. AIDS (acquired immunodeficiency syndrome)

AIDS is a term used for the most advanced stage of human immunodeficiency virus infection caused by HIV [73]. The virus attacks cells of the immune system, joint with them, and consequently destroys or reduces their responses that are by the term "Immunodeficiency" is used. AIDS is a very health-hazardous disease that affects the population of the entire globe [91]. If it remains untreated then the virus minimizes the number of CD4 cells (T cells) and hence damages the immune system which leads difficulty to fight off infections and other diseases as well. This opportunity for infections results in several different types of diseases, eg., TB, candidiasis, herpes simplex virus infection, or cancers, and signals that the person has AIDS [74, 88, 97]. HIV virus mainly spread through certain body fluids, sexual intercourse, pregnancy, breastfeeding, injecting drugs use, blood transfusion, etc [73, 91]. Unlike some other viruses, HIV can't be removed completely from the human body even it is treated timely. Therefore, once HIV enters your body, you have it for life long [90]. Currently, no effective cure exists for HIV but it can be controlled by proper medical care [76]. HIV infection doesn't mean the end of life, people can lead a healthy life for a long time by taking appropriate medical care. Anti-retroviral therapy (ART) effectively suppresses replication that restores the immune system and halts the onset and progression of the disease [89]. Hence, medication enhances both quality of life and longevity of people [75]. There were 37.9 million people (36.2 million adults, 1.7 million children<15 years) living with HIV, 1.7 million individuals are newly infected, 62% (23.3 million) of all people receiving ART, 21% (8.1 million) people didn't know their status and 53% achieved suppression of HIV with no riskin the world at the end of 2018 [77-79]. In June 2019, 24.5 million people were accessing antiretroviral therapy and between 2000- 2018, new HIV infections drop by 37% and HIV-related deaths reduce by 45%, with 13.6 million lives saved due to ART [79]. There are three stages of HIV infection. Symptoms occur according to these and severity varies from person to person [80]. The first stage is known as acute primary infection in which people can feel flue like symptoms, e.g., fever, body rash, sore throat, and swollen glands. headache. upset stomach, joint aches, and pains, muscle pain etc. These symptoms appear around one to four weeks after getting HIV in the body. The second stage is known as the asymptomatic stage. In this stage, HIV doesn't show any symptoms for up to 10 or even 15 years which depends on age and the general health of the person [80]. If people are untreated in this stage, then it will cause severe damage to the immune system and leads to the final stage of the AIDS stage also known as symptomatic HIV infection. Symptoms of the final stage are sudden weight loss; chronic diarrhea; night sweats; persistent cough; serious illness or disease, etc. More information about AIDS infection is given in Fig. 1.

Since the first case of AIDS emerged in 1986, mathematical modeling plays a crucial role to minimize the impact of the disease significantly [6, 71]. Mathematical models for HIV/AIDS with condoms use, treatment, and circumcision as preventive strategies are developed by several researchers and obtained male circumcision is a potentially effective control strategy for HIV/AIDS to help communities slow the development of the disease and it is more effective if implemented jointly with condom use [21-23]. Pre-exposure prophylaxis (PrEP) is used to minimize the number of HIV patients while ART and PEP are used to reduce HIV transmission and maintain the life span of HIV/AIDS patients [24, 25].The optimal control and effect of time delay on HIV/AIDS is also studied by the researchers and obtained how to minimize the virus concentration and treatment costs [26-28].

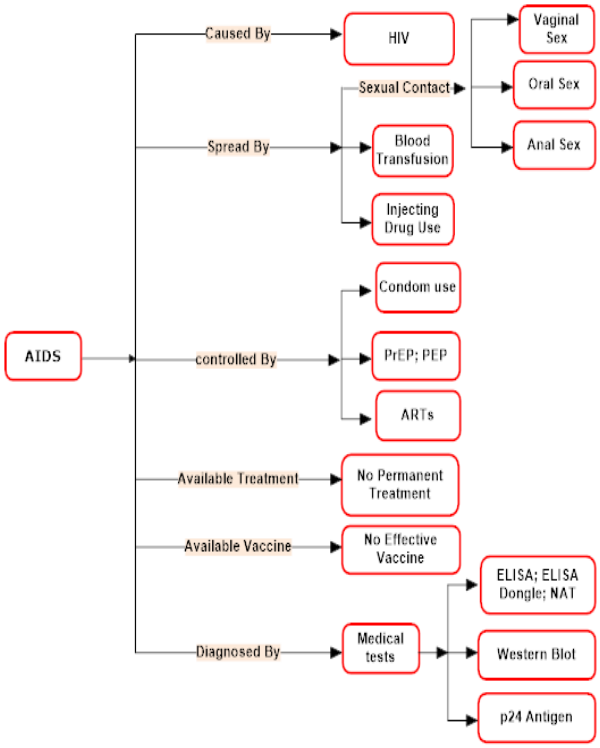

Fig. 1. Chart of AIDS infection.

B. Hepatitis B

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV) [81, 84, 115]. The Hepatitis B virus is more infectious than HIV that's by it is a major global health issue. It can cause both acute and chronic infections and symptoms are shown accordingly [83]. On the basis of health, the effect of this infection

varies from person to person. Many people didn't show any symptoms in their initial stage of the infection while others develop a rapid onset of sickness, yellowish, tiredness, dark urine, abdominal pain, etc. In the chronic stage also, most people don't have any symptoms however cirrhosis and liver cancer eventually developed [85]. An estimated 780,000 people die every year due to the consequences of hepatitis B, such as liver cirrhosis and liver cancer [82]. Vaccination is a very useful tool to reduce the impact of virus [86, 87]. Since the last two decades, mathematical modeling has been used frequently to study the transmission dynamics of Hepatitis B virus infection [29-31, 34]. A simple deterministic compartmental model developed by Anderson and May illustrate the effect of carriers on the transmission of the Hepatitis B virus [32]. Martin et. al proposed a mathematical model for viral dynamics in hepatitis B virus infection and obtained that treatment of chronic hepatitis B virus infection with lamivudine leads to a rapid and sustained decline of plasma virus level [33].A mathematical model of hepatitis B virus transmission with a vaccination strategy is proposed by Zhao et.al and it is suggested that vaccination coverage is the most important indicator for the elimination of hepatitis B virus transmission [35].Models of the hepatitis B virus with time delay and optimal control are developed by several researchers and found the global stability of the equilibrium points [31, 36, 37]. Available treatment, vaccine, affected organs of the body etc., are given in Fig. 2.

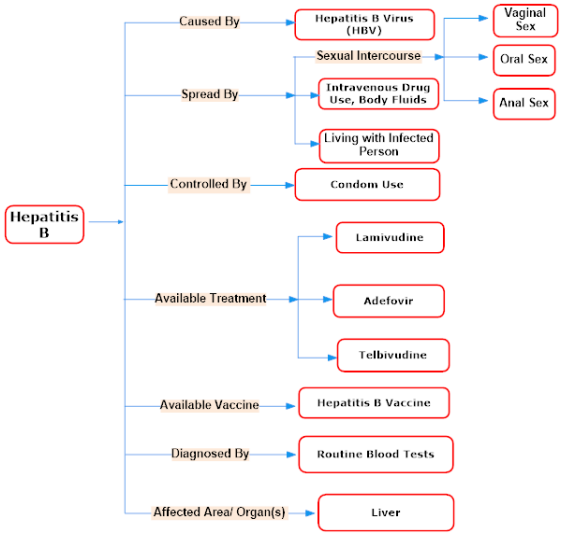

Fig. 2. Chart of Hepatitis B virus infection.

C. Human Papillomavirus Infection

It is a very common sexually transmitted infection (STI) caused by the human papillomavirus (HPV) which is a DNA virus from the papillomavirus family [94, 96]. There are several types of papillomavirus that affect the skin and moist membranes of the bodyand cause several cancers viz., cervical cancer, cancer of the anus, penis, vagina, vulva, etc. [93, 94, 96]. The virus can spread through skin-to-skin contact, sexual intercourse, sharing sex toys, etc.[92, 94, 96, 118]. Almost 30 types of HPV can affect the genitals and hence are known as genital HPV infections. Symptoms and effects of HPV infection will vary from person to person depending on which strain of HPV you have [93]. HPV vaccines can prevent the most common types of infection if they are used before the onset of sexual activity [94, 95, 97]. Here, it is also mentioned that the HPV vaccine only protects against certain strains of the virus which doesn't guarantee that the person will not develop an infection in the future. For more information about HPV infection see Fig. 3.

Mathematical models from individual and population points of view, will help decision-makers in the evaluation of various preventive measures for HPV and to deploy interactively to control cancer outcomes [38]. Poolman *et al*. proposed a mathematical model for the transmission of HPV and immunity to explore the effect of vaccination on the evolution of HPV and obtained that the balance of epidemiologic data suggests vaccination will reduce the infection [39]. More prevention strategies including vaccination for HPV are suggested by the researchers through mathematical modeling [40-42].

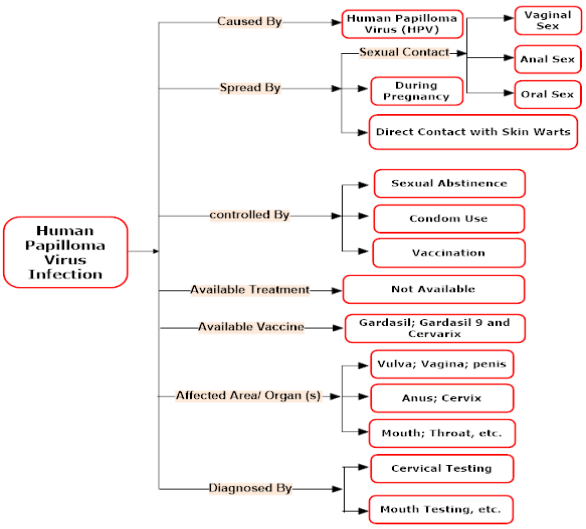

Fig. 3. Chart of human papillomavirus infection.

D. Candidiasis

Candidiasis is a fungal infection caused by Candida yeast which is a type of fungus. Candida albicans is the most commonly found fungal pathogen which affects humans [101]. Candida generally lives on the skin and inside the body such as in the mouth, throat, gut, and vagina without creating any problems [98]. When Candida affects the mouth, it is called thrush [102] and when it affects the vagina, it may be referred to as a yeast infection or vaginal candidiasis, or vulvovaginal candidiasis. Signs and symptoms for thrush include white patches on the tongue or other areas of mouth and throat while that for vaginal candidiasis include genital itching, burning, abnormal baginal discharge, and pain during sexual intercourse, etc. [99]. There are over 350 heterogeneous Candida species in which some of them have been implicated in human disease. Treatment is used to control the severity of the infection [100, 102]. The standard treatment of Candida infections consists of antifungal agents licensed from four different group, viz., polyenes, azoles, echinocandins, and nucleoside analogues. Treatment for the fungal also leads to the several side effects of the body, viz., skin irritation, oral ulcers, vomiting, headache, nausea, etc. [102]. See Fig.

4, for more information about candidiasis. There is lack of mathematical modeling related to candidiasis infection. A mathematical model for optimizing containment and control of candida parapsilosis fungemia among neonates in the outbreak setting is developed and uncertainty and sensitivity analysis are carried out by Anil A. Panackal and suggested that internal and external sources of candida can lead to invasive disease in neonates differentially.

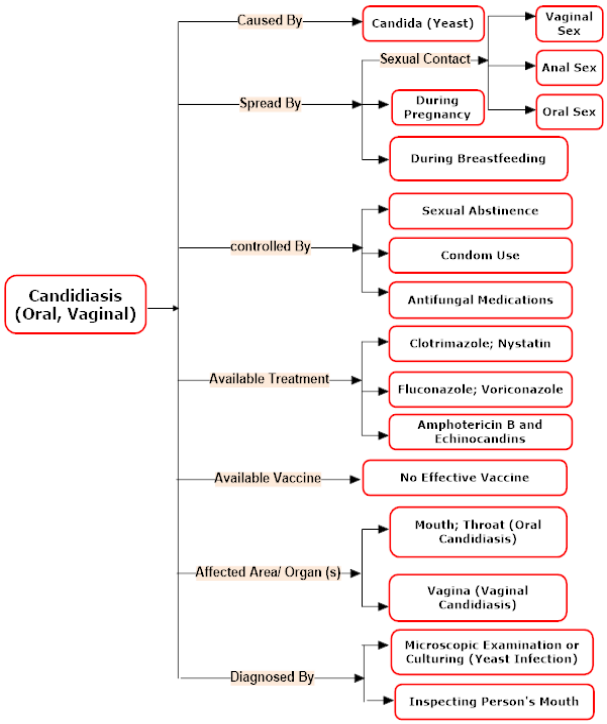

Fig. 4. Chart of candidiasis infection.

E. Syphilis

It is a sexually transmitted infection (STI) caused by the bacteria known as Treponema pallidum, a subspecies of pallidum [107]. It is also an infection that spread worldwide [104, 105, 107]. There are mainly four stages of the infection, viz., primary, secondary, latent, and tertiary. Routes of transmission and other important information are given in Fig. 5. Signs and symptoms of the infection vary depending on one of the four stages it presents. The first stage or primary syphilis lies between 10 days to 3 months with symptoms like a painless sore usually on the penis or vagina, mouth [104]; the second stage, or secondary syphilis begins a few weeks after the sore disappears while rashes are shown on the body, illness, weight loss or skin growths around the vulva. In third stage or latent stage, people don't show any symptoms for some years. In tertiary stage, syphilis can seriously damage heart, brain and nervous system [103]. If a person has an STI including syphilis then it increases the risk of getting HIV infection or other STDs (Sexually transmitted diseases) [106, 117]. Syphilis is easily treatable and curable in early stages [105, 107]. If remains untreated, it can have very serious complications. Several efforts have been made by the researchers to develop such a mathematical model which describes dynamics of the syphilis infection as much as possible. In this order, a mathematical model developed by Pourbohloul et al. to understand the impact of mass treatment on syphilis transmission suggested that mass treatment may not be an optimal strategy to prevent the transmission of the infection if complete coverage of high frequency transmitters can't be achieved and if mobility of the population is relatively high [43]. After the findings of their mathematical model, Miller and Zhao suggested that the development of an effective vaccine and health education leads to enhanced biological and behavioral protection against infection in high-risk population [44]. Mathematical models for the transmission dynamics of syphilis including MSM and HIV co-infection have been proposed by the researchers [45-48].

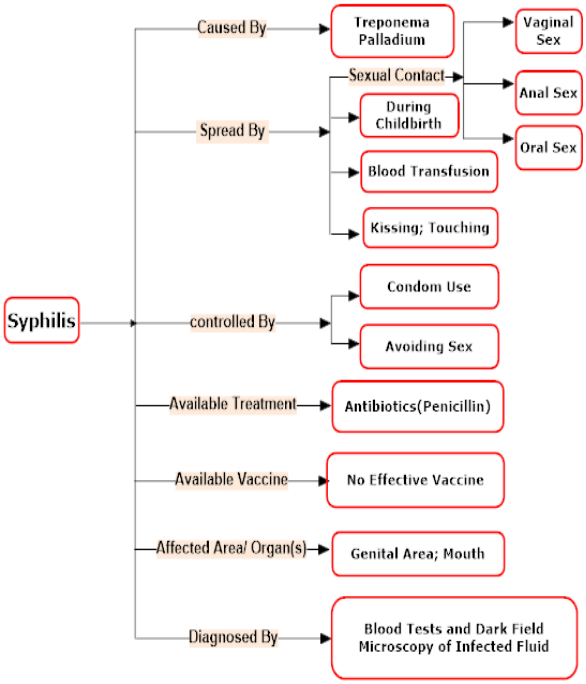

Fig. 5. Chart of syphilis infection.

F. Genital Herpes

Genital herpes is a chronic life-long viral infection caused by the herpes simplex virus (HSV) [109, 111]. HSV is of two types viz., HSV-1 and HSV-2 [108, 109, 111]. HSV-1 generally causes coled sores on mouth and lips while HSV-2 normally causes herpes around genitals anus or legs [108]. According to World Health Organization (WHO) an estimated 3.7 billion people below age 50 years have HSV-1 infection while that of 417 million people aged 15-49 years have HSV-2 infection globally [108]. Both herpes infections are mostly asymptomatic but can cause mild symptoms or painful blisters. HSV-1 is highly contagious infection commonly spread throughout the world transmitted through oral to oral or oral to genital contact [108, 109, 112, 113]. HSV-2 infection is exclusively a sexually transmitted infection which is spread throughout the world causing genital herpes. Infection caused by HSV-2 is lifelong and incurable. Genital herpes increases the risk of getting and spreading HIV infection [110, 112]. HSV-1 or HSV-2 along with HIV can leads to severe complications such as disseminated infection, hepatitis, keratitis or encephalitis, etc. [108, 111]. Antiviral medications are used to treat the people infected from HSV [110, 111]. Additional research is underway to develop more effective prevention

strategy or vaccine against both the infections [113]. Methods to diagnose Genital herpes and control strategies are shown in Fig. 6**.** Spicknall *et al*. 2019 [45] (reviews several mathematical models of HSV-2 for the development of effective vaccine. They compared each model's structure and assumptions as well as predicted vaccination impact [53]. Transmission dynamics of two strain herpes simplex virus is studied by Ibrahim et al. by developing mathematical model and obtained the equilibria of the models are globally asymptotically stable for special case and it is also shown that super infection increases the outbreak of HSV-2 [54]. Mathematical study of HIV and HSV-2 co-infection is done by Basak et al. and obtained that the reduction of the effective contact rate of HSV-2 can reduce the disease burden of co-infection [55]. Other mathematical models with drug resistance are developed by the researchers [56-58].

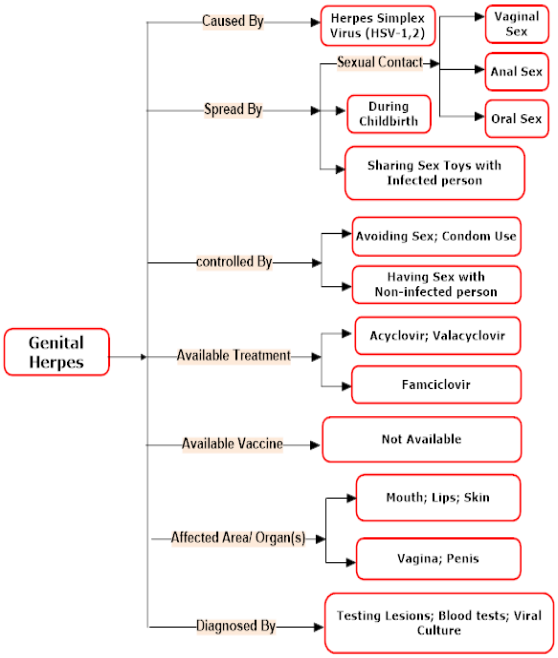

Fig. 6. Chart of genital herpes infection.

G. Chlamydia

Chlamydia is one of the most sexually transmitted infection caused by bacteria called Chlamydia trachomatis. Generally, it is an asymptomatic infection spreading worldwide. An estimated 131 million new cases of chlamydial genital infection occur annually. Chlamydia is easily curable but can make it dangerous to get pregnant if left untreated. The bacteria are normally found in infected semen and vaginal fluids and can be passed very easily through sexual intercourse, mother to unborn baby during pregnancy (Fig. 7). If someone is infected with any STI and chlamydia then it is more likely that the person is at high risk of getting HIV or pelvic inflammatory disease (PID) because of the weakness of immune system. Symptoms of the infection if shown, in women include pain or burning during urination, pain during sex or bleeding after sex, bleeding between periods or heavier periods, etc. while for men includes pain, discharge or bleeding in the anus pain or swelling in the testicles, white, cloudy or watery discharge form the penis. Although there is no vaccine available for the infection but antiviral medications are used to cure or control the infection. Turner et al. developed a realistic sexual network model of chlamydia transmission in Britain and suggested that the model structure is flexible and is broadly applicable to other developed world settings and provides a practical tool for health decision makers [49]. Mathematical analysis of chlamydia model with pulse vaccination in a random environment is studied by Samanta and Bera and obtained that if impulsive vaccination rate is larger than some critical values, then chlamydia disease can be prevented from generating endemic [50]. Mathematical models regarding the impact of screening programmers on chlamydia infection is also studied by the researchers and concluded that longer duration of the asymptomatic period leads to a more pronounced impact of screening programmer and continuous opportunistic screening at with high uptake rates could significantly reduce the chlamydia prevalence within a few years [51, 52].

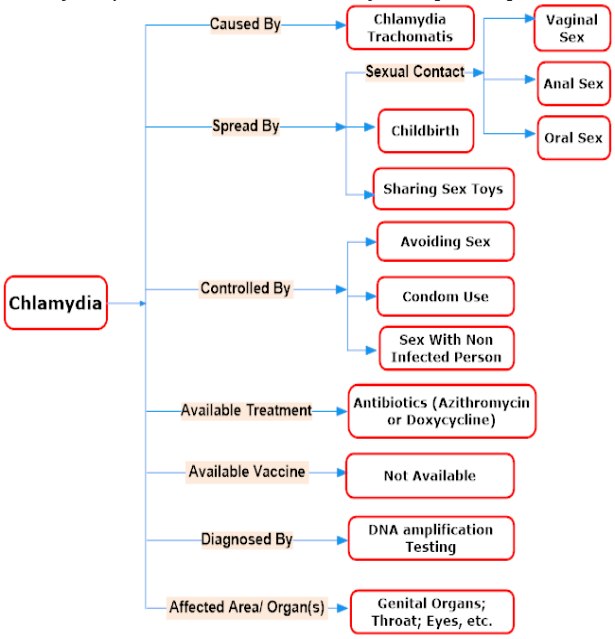

Fig. 7. Chart of chlamydia infection.

H. Gonorrhea

Gonorrhea or clap caused by the bacteria, Neisseria gonorrhoeae or gonococcus (Fig. 8) is a most influential sexually transmitted infection. It is the second most common STIs in North America. In 2018, a total number of 583, 405 cases of gonorrhea were reported in the US with the rate of 179.1 cases per year. This infection is often asymptomatic in women while symptomatic in men. When it is symptomatic, symptoms in men includes urethral discharge and/or itching, testicular or rectal pain while in women includes vaginal discharge, abnormal uterine bleeding, lower abdominal and/or rectal pain etc. It can be easily treated and cured with a short course of antibiotics if the treatment is done at the right time. Antibiotics are given to the infected person either orally or through injection. If left untreated, it may cause infertility, PID, other health issues or STIs. Currently, there is no effective vaccine available to cure the infection while research is going on to make a best suitable for humans [116]. The first mathematical model for gonorrhea infection and modeling growth processes was

developed by Cooke and Yorke [60]. The spread of gonorrhea in the population is very no-uniform and hence a deterministic mathematical model in non-homogeneous population is developed by James A. Yorke, and found out that the disease will die out either for all positive initial disease levels or for none which depends on contact rates and lengths of infectious period [59]. Models of gonorrhea transmission with control strategies viz., treatment, condom use are studied by various researchers and found out fruitful outcomes [61-65].

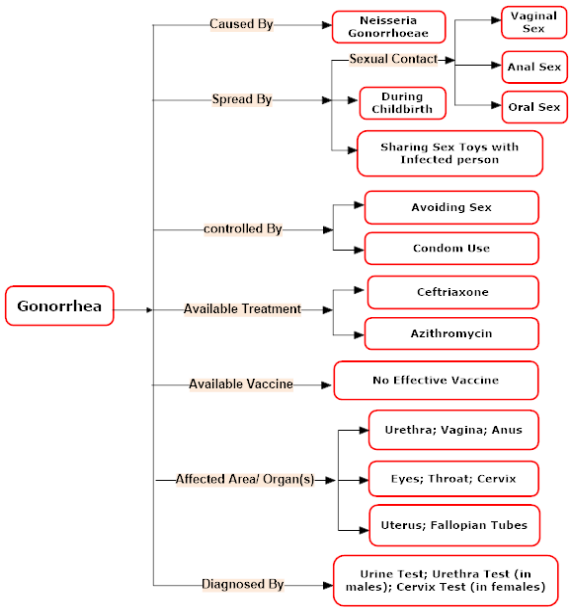

Fig. 8. Chart of gonorrhea infection.

I. Trichomoniasis

Trichomoniasis (or Trich) is a commonly found STI all around the world caused by a tiny protozoan parasite known as Trichomoniasis vaginalis. The parasite is mainly spread through sexual activity as it found in the vagina and urethra or head of the penis. Most people infected with the infection do not show any symptoms and can be undetected for several years. If symptoms are shown by the person, it includes itching, burning, redness of the genitals, discomfort during urination, change in their discharge form vagina or penis. The people can be cured from the infection by using vaccine as well as treatment provided that if taken right medications. Antibiotics may be used by the infected person for treatment point of view while in vaccination point of view. The infection may lead to severe complications for people and increases the risk of getting and spreading other STIs, if untreated. The Fig. 9 exhibit more information about trichomoniasis infection. The transmission dynamics of trichomoniasis vaginalis was mathematically studied by Bhunu and Mushayabasa and shown that treatment is able to control *Trichomonas baginalis* infection which suggests an effective control of trichomoniasis rests in encouraging and persuading sexual partners of those displaying symptoms to seek treatment [66]. Co-infection models of trichomonas vaginalis and HIV are studied by several researchers and obtained that trichomonas vaginalis and HIV fuel each other [67, 68]. Control strategies viz., treatment condom use, and counseling of individuals with trichomonas vaginalis symptoms can leads to the effective control or elimination of the HIV from population if their effective measure is high [68].

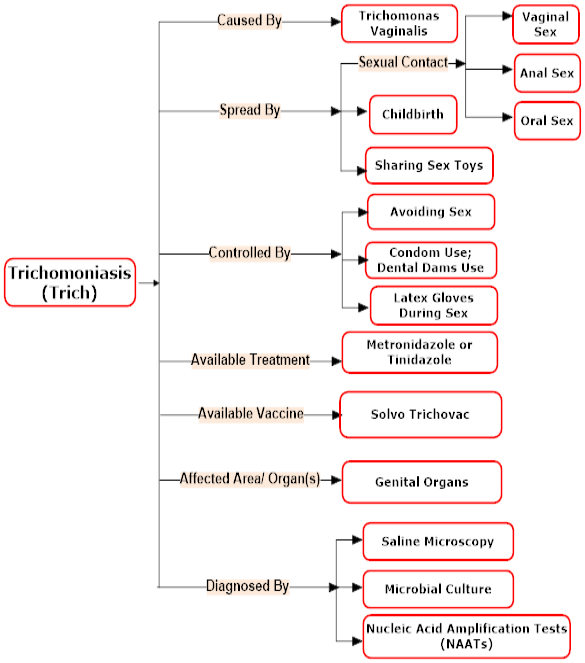

Fig. 9. Chart of trichomoniasis infection.

III. RESULTS AND DISCUSSION

An important question in mathematical epidemiology is what type of information influences the behavior of people during a disease outbreak in a particular area and how to include all these in a mathematical model. Mathematical models of HIV/AIDS with some control strategies like pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), sex education, counseling, HIV test before marriage, etc., are required to include in mathematical models. Mathematical models that include intracellular processes of the Hepatitis B virus life cycle, and immune response are needed like those models developed for the control of HIV [34]. It is required to incorporate more preventive measures other than vaccination in the modeling of human papillomavirus infection such as condom use, social awareness, etc. We have found that there is a lack of mathematical models for candidiasis infection that includes treatment, immune response, etc. Mathematical models for syphilis with co-infection with other STDs and stage-structured models are required to be developed so that the burden of the infection can be reduced [48]. To capture the impact and cost-effectiveness of the HSV vaccine, other disease outcomes directly or indirectly caused by HSV infection like HSV-1, neonatal herpes, and HIV should be incorporated into mathematical models. Some models including sex and sexual activity, heterogeneous infection rate by age, sensitivity, and uncertainty analysis is also needed to be developed in order to resemble more closely the transmission dynamics of the infection [53]. The effect of time delay and optimal control should also be discussed through mathematical modeling for chlamydia infection. Co-infection model for gonorrhea and trichomoniasis with other STDs is to be developed by

the researchers so that the co-infection caused severity in terms of infertility, PID, etc. can be controlled.

IV. CONCLUSION

In mathematical epidemiology, understanding the influence of information on people's behavior during disease outbreaks and incorporating it into models is crucial. HIV/AIDS models should include strategies like PrEP, PEP, education, counseling, and premarital HIV testing. Similarly, for Hepatitis B, models need to consider intracellular processes and immune response. Preventive measures beyond vaccination, such as condom use and awareness campaigns, should be included in HPV models. Mathematical models for candidiasis, syphilis, and co-infections require development, along with incorporating outcomes like HSV-1, neonatal herpes, and HIV. Models accounting for sexual activity, age-related infection rates, and time delay can enhance transmission dynamics understanding. Co-infection models for gonorrhea and trichomoniasis are needed to address infertility and PID severity.

V. FUTURE SCOPE

New mathematical models incorporating behavioral influences, control strategies (PrEP, PEP, education, counseling), immune response, preventive measures (condom use, awareness), treatment, and co-infections can provide more insights into the pattern of infectious disease and also optimization models for various diseases like HIV/AIDS, Hepatitis B, HPV, candidiasis, syphilis, HSV, chlamydia, gonorrhea, and trichomoniasis can be used to reduce infection burden and improve interventions.

Acknowledgements. The authors would like to express their sincere thanks to the anonymous referee for valuable constructive comments, and suggestions which improved this paper.
Conflict of Interest. None.

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How to cite this article: Prakash Narayan, Kunwer Singh Mathur, Bhagwan Kumar and Rashmi Mathur (2023). A General Review of Sexually Transmitted Diseases (STDs) in Theoretical and Mathematical Modeling Aspects. *International Journal on Emerging Technologies, 14*(1): 42–51.