Confluence Journal of Pure and Applied Sciences (CJPAS)
Faculty of Science, Federal University Lokoja, Kogi State, Nigeria

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

MODELING THE ROLE OF WILD RODENTS IN THE DYNAMICS OF TRANSMISSION OF HEPATITIS E VIRUS WITH ZOONOTIC POTENTIAL

Osanyinlusi S. A.*[1], Are E. B.[2], Bakare, E.A.[2], and Omilabu S. A[3].

[1]*Department of Microbiology, Federal University OyeEkiti, Nigeria*
[2]*Department of Mathematics, Federal University OyeEkiti, Nigeria*
[3]*Virology Unit, Central Research Laboratory/Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria*

ABSTRACT

We developed a compartmental deterministic model to analyze the zoonotic potentials of HEV transmission. This model incorporates the vector-host system together with the environmental reservoir of HEV. Classification of the population also included the possible variance of the dynamics of HEV between pregnant women and non pregnant humans. An empirical study was also carried out to establish and identify a common viable host, in this case rat. The reproduction number (R_o) which is a threshold value was calculated using the next generation matrix method, which can be used to control the outbreak of HEV. Results obtained from the empirical study were used to simulate the model. The graphs show clearly that the model is valid and can be used to fit data, as these results generally compare well with existing results in literature.

Keywords: Hepatitis E virus, Rats, Pregnant women, Mathematical model, Reproduction number

1.0 INTRODUCTION

Hepatitis E virus (HEV), the etiological agent of acute viral hepatitis E is the only member of the genus Hepevirus and family *Hepeviridae*. It a non-enveloped, positive-sense, single-stranded RNA virus measuring approximately 27-34 nm in diameter. The genome of HEV is made up of three open reading frames (ORFs). ORF1 encodes non-structural proteins such as protease, helicase, and RNA-dependent RNA polymerase; ORF2 encodes the capsid protein, which aids virus cell entry and reaction to neutralizing antibodies; and ORF3 encodes a phosphorylated protein which mediates virus release (Yamada *et al.,* 2009). Annually, an estimated 20 million hepatitis E infections, with over 3 million symptomatic cases, and 57,000 hepatitis E-related deaths are reported globally (WHO, 2017). Infections caused by hepatitis E virus is usually self-limiting resolving within 4–6 weeks, but may progress to a fulminant hepatic failure that may resort to death in certain high-risk groups, like pregnant women and elderly patients with inherent liver disease (Siddharth *et al.,* 2015).

Infection is usually contracted by the fecal-oral route through consumption of contaminated food and water. Young adults between 15 and 45 years have higher risk of infection, but the disease is notably fulminant in pregnant women, with 20-30% fatality. Other modes of transmission have been reported include: food-borne transmission from ingestion of infected animal products, human-to-human transmission in developed countries through transfusion of infected blood products from viremic donors, and vertical transmission from infected pregnant women to fetus(WHO, 2017, Siddharth *et al.,* 2015, Lhomme *et al.,* 2013). The transmission of HEV has extended widely to incorporate zoonotic transmission from wild and domestic animals including pigs, deer, boar, mongooses, rabbits as

***Corresponding Author**

How to cite this paper: Osanyinlusi S. A., Are E. B., Bakare, E.A., & Omilabu S. A. (2018). Modeling the role of wild rodents in the dynamics of transmission of hepatitis e virus with zoonotic potential. *Confluence Journal of Pure and Applied Sciences (CJPAS), 2(1), 39-47.*

well as rodents, (Mulyanto *et al.,* 2013; Li *et al.,* 2013; Lack *et al.,* 2012; Nidaira *et al.,* 2012; Johne *et al.,* 2010; Sonoda *et al.,* 2004; He *et al.,* 2002). For instance, HEV genotype 3 was first isolated from swine specimens in the United States in 1997. Indirect evidence of zoonotic transmission has been established through increased seroprevalence studies of HEV in swine handlers as a result of contact with infected animals (Okano *et al.,* 2014; Liang *et al.,* 2014; Lee *et al.,* 2013; Wiratsudakul *et al*., 2012; Levin *et al.,* 1997). The possibility of rodents transmitting HEV to humans is yet to be fully established. However, HEV strains correlating to human pathogenic HEV strains have been reported in rat, rabbit, and mongoose populations (He *et al*., 2002; Johne *et al*., 2012; Lack *et al*., 2012; Mulyanto *et al*., 2013; Li *et al*., 2013; Nidaira *et al.,* 2012; Sonoda *et al*., 2004). Yet, their role in transmission to humans is still being investigated. Wildlife species including rodents have continuously been linked to the emergence of zoonotic diseases. The dynamics of zoonotic disease transmission involving wildlife are deemed complex and non-linear (Lorenzo *et al.,* 2012). Mathematical models have been highly helpful in understanding the dynamics of a number of viral diseases including hepatitis E, hepatitis B, hepatitis A etc. (Subrat *et al*., 2013). Oftentimes, the dynamics as well as the factors responsible for outbreaks of infectious diseases are better understood using mathematical models that are fit to data (Diekmann and Heesterbeek, 2000). However, other models have employed differential equations with distinct compartments to better understand the transmission of zoonotic vector-borne diseases (Subrat *et al*., 2013). Mercer and Siddiqui, (2011) included both the environmental reservoir and person-to-person spread in their model designed for hepatitis E virus transmission dynamics, making use of other parameters derived from knowledge of the viral pathogen. The transmission dynamics in the human host or reservoir hosts has being the focus of most works, with limited consideration for the coupled dynamics of spillover transmission to humans (Lloyd-Smith *et al.,* 2009).

In this study, we employed mathematical modeling tools to understand the dynamics of hepatitis E virus in wild rodents, the environmental reservoir host as well as possible zoonotic transmission to humans.

2.0 EMPIRICAL STUDY

The potential of rats captured within human dwellings harboring infectious HEV was investigated. Rodents comprising brown rats (*R. norvegicus*) and Musk shrew (*C. dolichura*) were captured, sacrificed by cervical dislocation and viral RNA was extracted from blood, liver, kidney, heart and lung tissues of the captured rodents. Purified RNA were amplified using a nested reverse transcription polymerase chain reaction (RT-PCR) with primers targeting conserved regions of the open reading frame 1 (ORF1) of the HEV genome. The study detected HEV RNA from the following organs of *R.norvegicus*; blood (6), lungs (5), heart (5), liver (4) &kidney (4) with an overall prevalence rate of 40% (24 of 60) and one positive blood sample from *C.dolichura (unpublished data)*. Similarly, HEV-specific antibodies have been reported from Countries including Japan, USA, Brazil, India and Vietnam in various rodents including black rats *(Rattus rattus),* brown rats *(Rattus norvegicus)*, cotton rat *(Sigmodon hispidus)* as well as deer mouse *(Peromyscus maniculatus)* (Hirano *et al.,* 2003, Meng *et al.,* 2002, Widen *et al.,* 2014). Also, anti-HEV-specific antibody in wild rodents as well as the detection of an HEV-like virus from Norway rats in Germany has been reported (Johne *et al.,* 2010). Zoonotic hepatitis E virus has equally been detected in French and Norway rats (*R. norvegicus*) captured very close to pig farm (Kanai *et al*., 2012).

3.0 MODEL DEVELOPMENT

The model was developed such that all the vital players in the transmission dynamics of HEV were considered, the human population at any time t,

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

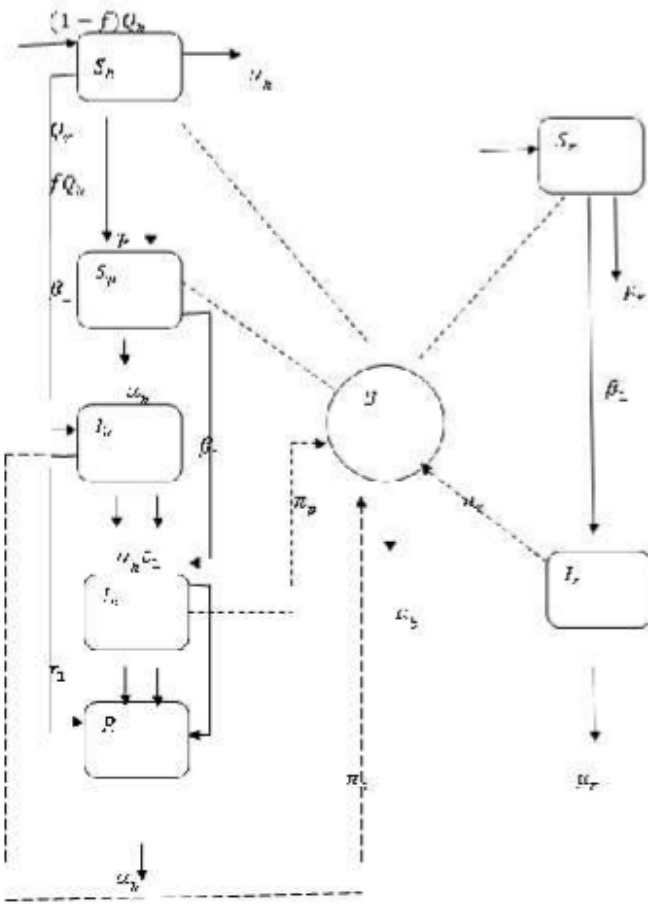
population$N_r(t) = S_h(t) + I_r(t)$, susceptible rats and Infectious rats, and the pathogen population is given as $B(t)$. $Q_h$is the recruitment rate of humans,Q_r the recruitment rate of rats,f is the proportion of pregnant women, hence, $(1-f)Q_h$ is the recruitment rate of non pregnant humans. The force of infection $\lambda = \frac{\beta_1 B(t)}{\varepsilon + B(t)}$ where β_1 is the effective contact rate of the susceptible population with the environmental reservoir.

Below are the symbols used and their descriptions.

Model parameters	Description
μ_h	Human natural mortality
μ_r	Rats natural mortality
μ_ε	Natural deactivation rate of HEV
r_1	Recovery rate in humans
r_2	Recovery rate for pregnant women
e_1	HEV mortality rate in humans
e_2	HEV mortality rate in pregnant women
π_p	Net contribution of infected pregnant women to HEV population
π_h	Net contribution of infected humans to HEV population
π_r	Net contribution of infected rats to HEV population
ρ	Rate at which humans become pregnant
Q_r	Recruitment rate of rats
Q_h	Recruitment rate of humans
f	Proportion of pregnant women
λ	Force of infection
b	Small parameter <<1

The schematic of transmission is presented as below.

3.1 SCHEMATIC OF THE SYSTEM



3.1.1 THE MODEL ASSUMPTIONS

- No veridical transmission in both rats and humans.
- Permanent immunity after recovery.
- There is natural deactivation of HEV in the environment.
- There is natural death rate for both humans and rats.
- Sexual transmission is not included.

3.2 THE MODEL EQUATION

$$\frac{dS_h}{dt} = (1-f)Q_h - S_h(\lambda + \rho + \mu_h)$$

$$\frac{dS_p}{dt} = fQ_h + S_h\rho - S_p(\mu_h + \lambda)$$

$$\text{x} \quad \frac{dI_h}{dt} - S_h\lambda - I_h(\mu_h + e_1 + r_1)$$

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

$$\frac{dI_p}{dt} = S_p\lambda - I_p(\mu_h + \varepsilon_2 + \tau_2)$$

$$\frac{dR}{dt} = \tau_1 I_h + \tau_2 I_p - \mu_h R$$

$$\frac{dS_r}{dt} = Q_r - S_r(\mu_r + \lambda)$$

$$\frac{dI_r}{dt} = S_r\lambda - \mu_r I_r$$

$$\frac{dB}{dt} = \pi_p I_p + \pi_h I_h + \pi_r I_r - \mu_b B$$

Where $\lambda = \frac{\beta_2 B}{b+B}$

$S_p(0) = S_{p0}, S_h(0) = S_{h0},$

$I_p(0) = I_{p0}, \quad I_h(0) = I_{h0},$

$R(0) = R_0, \quad I_r(0) = I_{r0},$

$S_r(0) = S_{r0}, \quad B(0) = B_0$

4.0 MODEL ANALYSIS

4.1 Disease Free Equilibrium Point

Disease Free Equilibrium (DFE) is the state at which the population is free from HEV. The DFE point of the model has been obtained to be

$(S_h^*, S_p^*, I_h^*, I_p^*, R^*, S_r^*, I_r^*, B^*) = (\frac{(1-f)Q_h}{(\mu+\mu_h)}, \frac{(1+\mu_h)Q_h f}{\mu_h(\mu+\mu_h)}, 0, 0, 0, \frac{Q_r}{\mu_r}, 0, 0)$, In the absence of HEV there will be no infection in the population, we then have that $I_h^* = I_p^* = R^* = I_r^* = B^* = 0$

Solving $(1-f)Q_h - S_h(\lambda + \mu + \mu_h) = 0$ and $fQ_h + S_h\mu - S_p(\mu_h + \lambda) = 0$ for S_h and S_p, yield $S_h = \frac{(1-f)Q_h}{(\mu+\mu_h)}$ and $S_p = \frac{(1+\mu_h)Q_h f}{\mu_h(\mu+\mu_h)}$ respectively.

4.2 The Basic Reproduction Number

The basic reproduction number R_0, is of high epidemiological importance. R_0 can be used to determine and control epidemics. When $R_0 < 1$ there will be little or no risk of an epidemic, but when $R_0 > 1$ the disease will become endemic R_0 can simply be defined as the expected number of infections generated by a single index case, throughout his or her entire infectious period, in a large and fully susceptible population (Diekmann and Heesterbeek, 2000)

Mathematically, R_0 can be calculated using the Next generation operator method. We obtain a matrix F, which is the new infection term, and V, the other transfer terms. R_0 is the spectral radius of the next generation matrix FV^{-1}, where V^{-1} is the inverse of V(Ajelli, 2008).
For the above system,

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

$$F=\begin{pmatrix} 0 & 0 & 0 & \frac{(1-f)Q_h}{r+m_h} \\ 0 & 0 & 0 & \frac{(1+m_h)fQ_i}{(r+m_h)m_h} \\ 0 & 0 & 0 & \frac{Q_h}{m_r} \\ p_h & p_h & p_h & 0 \end{pmatrix} \quad V=\begin{pmatrix} \eta_h+e_2+r_2 & 0 & 0 & 0 \\ 0 & m_h+e_2+r_2 & 0 & 0 \\ 0 & 0 & m_r & 0 \\ 0 & 0 & 0 & m_b \end{pmatrix}$$

The reproduction number is obtained as:

$$R_c = \frac{\sqrt{m_1\mu^3{}_h + \pi_r Q_r m_2 - \mu^2{}_r Q_h \mu^2{}_h m_3 + Q_r m_4 - \mu^2{}_r \mu_h m_5 + m_6}}{m_7 m_8 m_9 m_{10}}$$

Where

$$m_1 = (\mu_h + \mu)\mu_b(\mu_h + \varepsilon_1 + \tau_1)(\mu_h + \varepsilon_2 + \tau_2)\pi_r Q_r \mu^4{}_h + \pi_r Q_r(\tau_2 + \varepsilon_1 + \varepsilon_2 + \tau_1 + \mu)$$

$$m_2 = (\tau_2 + \varepsilon_1 + \varepsilon_2 + \tau_1)\mu + (\tau_1 + \varepsilon_1) + (\varepsilon_2 + \tau_2)$$

$$m_3 = -((\pi_h - \pi_p)f - \pi_h)$$

$$m_4 = \mu\pi_r(\tau_1 + \varepsilon_1)(\varepsilon_2 + \tau_2)$$

$$m_5 = -f\pi_p\varepsilon_1 + \pi_h(f-1)\varepsilon_2 + \pi_h(f-1)\tau_2 - f\pi_p(r+1)Q_h$$

$$m_6 = \mu^2\mu\pi_p Q_h(\tau_1 + \varepsilon_1)$$

$$m_7 = \mu_r b\mu_b\mu_h$$

$$m_8 = (\mu_h + \mu)$$

$$m_9 = (\mu_h + \varepsilon_1 + \tau_1)$$

$$m_{10} = (\mu_h + \varepsilon_2 + \tau_2)$$

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

5.0 NUMERICAL SIMULATIONS AND DISCUSSION OF RESULTS

Numerical simulations were carried out using MAPLE 18, a mathematical package used for analysis and simulations of mathematical models. Some initial values are assumed for the stated variables as follows;

$S_p(0) = 500, S_h(0) = 4000,$

$I_p(0) = 80, \quad I_h(0) = 100,$

$A(0) = 0, \quad I_v(0) = 30,$

$S_v(0) = 100, \quad B(0) = 985$

The following results are obtained.

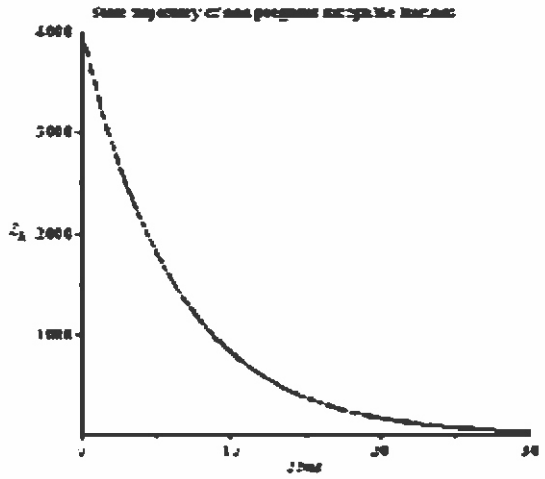


Figure 1

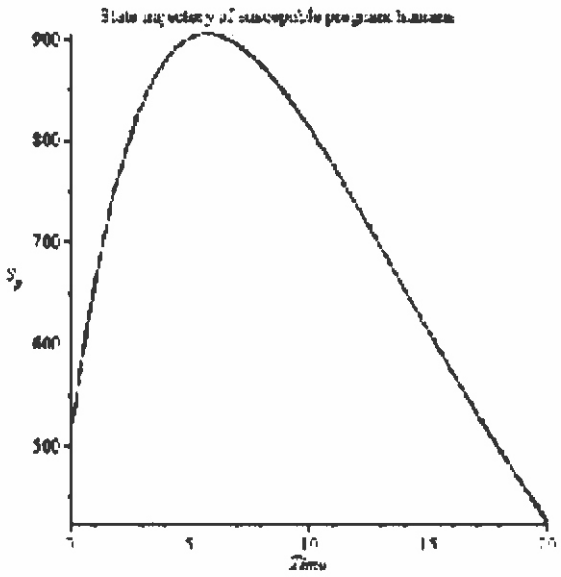


Figure 2

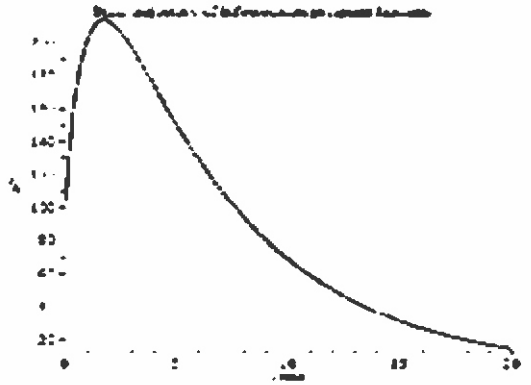


Figure 3

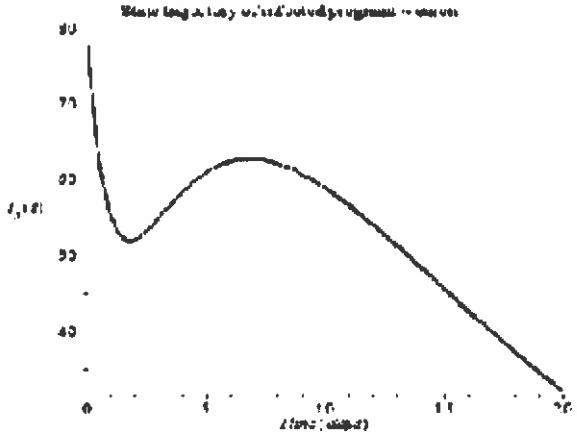


Figure 4

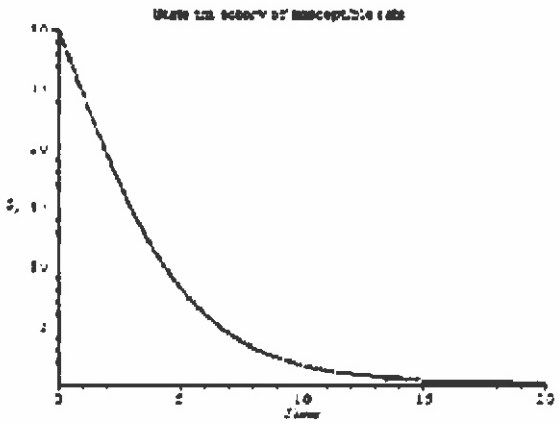


Figure 5

Vol. 2, No. 1, June 2018
ISSN: 2616-1303 | **Web:***www.cjpas.fulokoja.edu.ng*

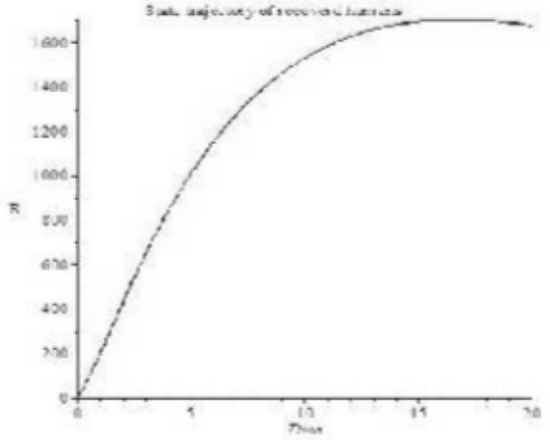


Figure 6

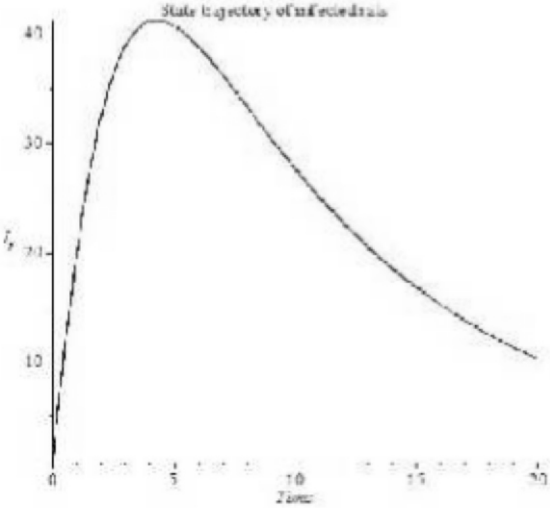


Figure 7

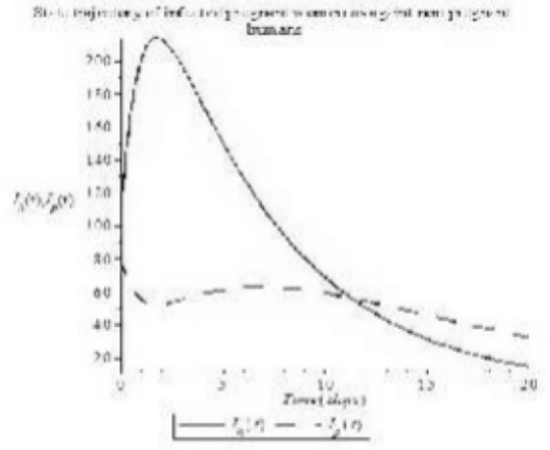


Figure 8

It was observed in figure 1 that when there was free mixing between susceptible populations and the infected, there will be a gradual decline in susceptible human population as more people get exposed to HEV. This is mathematically reasonable because of the mass action incidence. Within a short period of time, say 30 days, the total number of susceptible humans to HEV declines gradually. Figure 2 shows the trajectory of susceptible pregnant women to HEV with time, the population of susceptible pregnant human increases gradually due to recruitment from the susceptible human population, and thereafter decline as members of the susceptible pregnant humans becomes exposed and infected with HEV. In Figure 3, we observe a gradual rise in the population of infected non pregnant human, this is then preceded by a decline as people recover and acquire immunity to HEV. In Figure 4, there was a marked disparity in the dynamics of HEV transmission in infected pregnant women and infected non pregnant human, the population of infected pregnant women decreased sharply, and thereafter rose to a peak, this was followed by another decline. These movements are a pointer to the fact that the transmission dynamics of HEV differs for different risk groups. Figure 5 showed the population of recovered individuals, it also showed that people tend to get some kind of immunity to HEV as individuals tend to remain in the recovered class. Figure 6 showed how quickly susceptible rates were infected with HEV when they continued to interact with contaminated environments and infected rates.

In Figure 7, the trajectory of infected rats showed a sharp increase but failed to decline to a point of extinction. This is a pointer to the fact that rats continuously harbor HEV although the virus doesn't kill them. Figure 8 compared the population of infected pregnant women with infected non-pregnant humans. It showed clearly the disparity between the dynamics of HEV in pregnant humans and those that are not.

6.0 SUMMARY AND CONCLUSION

In this work an empirical cross-sectional study was carried out to determine the prevalence of HEV in rats around Alimosho local Government area of Lagos state, Nigeria. A compartmental mathematical model has also been proposed to boost the understanding of HEV infection in both pregnant and non pregnant humans. This model is presented in a flow chat and also expressed as eight compartmental systems of first order ordinary differential equations. The basic reproduction

number R_o which is a threshold value used to determine the average strength of infectiousness of an individual was derived by the next generation matrix method. By employing some parameter values in literature and those obtained from the empirical study, the model was simulated using MAPLE 18, mathematical software. The results as presented in the graphs show the dynamics of infection in non-pregnant humans, pregnant humans, rats and the environmental reservoir of HEV. The trajectory of the graph shows that the model is mathematically valid and biologically meaningful. This model can be adopted by investigators for the purpose of further studies on HEV. It can also be used to fit data for possible futuristic predictions of HEV epidemics. Further studies can be done by carrying out sensitivity analysis on the R_o to determine the best control strategies to employ to reduce the possibility of HEV epidemics.

REFERENCES

He J., Innis B. L., Shrestha M. P., Clayson E. T., Scott R. M., Linthicum K. J.(2002). Evidence that rodents are a reservoir of hepatitis E virus for humans in Nepal. *J Clin Microbiol*; **40**:4493e8.

Hirano M., Ding X., Li T. C., Takeda N., Kawabata H., Koizumi N., Kadosaka T., Goto I., Masuzawa T. (2003). Evidence for widespread infection of hepatitis E virus among wild rats in Japan. *Hepatol Res.;* **27**: 1–5.

Johne R., Dremesk P., Reetz J., Heckel G., Hess M., Ulrich R. G. (2014). Hepeviridae: An expanding family of vertebrate viruses. *Infect Genet Evol*;**27**:212e29.

Johne R., Pienge-Bo¨nig A., Hess M., Ulrich R. G., Reetz J., Schielke A. (2010). Detection of a novel hepatitis E-like virus in faeces of wild rats using a nested broad-spectrum RT-PCR. *J Gen Virol*; **91**:750e8.

Kanai Y., Miyasaka S., Uyama S., Kawami S., Kato-Mori Y., Tsujikawa M., Yunoki M., Nishiyama S., Ikuta K and Hagiwara K. (2012). Hepatitis E virus in Norway rats *(Rattus norvegicus)* captured around a pig farm. *BCM Research Notes.;***5**: 4.

Kathleen A. Alexander, Bryan L. Lewis, MadhavMarathe, Stephen Eubank, and Jason K. Blackburn (2012). Modeling of Wildlife-Associated Zoonoses: Applications and Caveats. *Vector-Borne And Zoonotic Diseases* **12 (12)**; 1-14

Lack J. B., Volk K., Van Den Bussche R. A. (2012). Hepatitis E virus genotype 3 in wild rats, United States. *Emerg Infect Dis* ;**18**: 1268e73.

Lee J. T., Shao P. L., Chang L. Y., Xia N. S., Chen P. J., Lu C. Y. (2013). Seroprevalence of hepatitis E virus infection among swine farmers and the general population in rural Taiwan. *PLoS One*; **8**:671-80. http://www.ncbi.nlm.nih.gov/pubmed/23840620.

Levin S. A., Grenfell B., Hastings A. (1997). Mathematical and computational challenges in population biology and ecosystems.. *Science*; 8: 275:334.

Lhomme S., Dubois M., Abravanel F., Top S., Bertagnoli S., Guerin J. L. (2013) Risk of zoonotic transmission of HEV from rabbits. *J Clin Virol* ;**58**:257e62.

Li W., Guan D., Su J., Takeda N., Wakita T., Li T. C., (2013). High prevalence of rat hepatitis E virus in wild rats in China. *Vet Microbiol* ;**165**:275e80.

Liang H., Su S., Deng S., Gu H., Ji F., Wang L. (2014). The prevalence of hepatitis E virus infections among swine, swine farmers and the general population in Guangdong Province, China. *PLoS One* ;**9**:e88106. http://www.ncbi.nlm.nih.gov/pubmed/24520348.

Lloyd-Smith J. O., George D., Pepin K. M. (2009). Epidemic dynamics at the human-animal interface. *Science*; **326**:1362.

Lorenzo P., Frank B., and Pieter T. (2012). Reproduction numbers for epidemic models with households and other social structures, 1. Definition and calculation of R math. *Biosci* **235(1):**85-97 doi:10.1016/j.mbs.2011.10.009

Meng X. J., Wiseman B., Elvinger F., Guenette D. K., Toth T. E., Engle R. E., Emerson S. U., & Purcell R. H. (2002). Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries. *J ClinMicrobiol*.; **40**: 117–122.

Mulyanto, Depamede S. N., Sriasih M., Takahashi M., Nagashima S., Jirintai S. (2013) Frequent detection and characterization of hepatitis E virus variants in wild rats (*Rattus rattus*) in Indonesia. *Arch Virol* ;**158**:87-96.

Nidaira M., Takahashi K., Ogura G., Taira K., Okano S., Kudaka J. (2012). Detection and phylogenetic analysis of hepatitis E viruses from mongooses in Okinawa, Japan. *J* Vet *Med Sci*; **74**:1665e8.

Okano H., Nakano T., Sugimoto K., Takahashi K., Nagashima S., Takahashi M., (2014) High genomic similarity between European type hepatitis E virus subgenotype 3e strains isolates from an acute hepatitis patient and a wild boar in Mie, Japan. *Hepatol Res* ;**44**:694-9.

Siddharth S., Susanna K. P. Lau, Patrick C.Y. Woo (2015). Hepatitis E: A disease of reemerging importance. *Journal of the Formosan Medical Association*; **1**(10); pp1-14

Sonoda H., Abe M., Sugimoto T., Sato Y., Bando M., Fukui E. (2004) Prevalence of hepatitis E virus (HEV) infection in wild boars and deer and genetic identification of a genotype 3 HEV from a boar in Japan. *J Clin Microbiol* ;**42**:5371e4.

Subrat Kumar, Subhra Subhadra, Bhupinder Singh, B. K. Panda. (2013). **Hepatitis E virus: the current scenario. International Journal of infectious Disease. 17(4) e228-e233.**

World Health Organization (WHO) Fact Sheet, (2017). Hepatitis E virus. http//:www.who.int/mediacentre/factsheets/fs280/en.

Widen F., Ayral F., Artois M., Olofson A., and Lin J. (2014). PCR detection and analysis of Potentially zoonotic Hepatitis E virus in French rats. *Virology Journal.;***11**: 90

Wiratsudakul A., Sariya L., Prompiram P., Tantawet S., Suraruangchai D., Sedwisai P. (2012). Detection and phylogenetic characterization of hepatitis E virus genotype 3 in a captive wild boar in Thailand. *J Zoo Wildl Med*;**43**: 640-4.

Yamada K., Takahashi M., Hoshino Y., Takahashi H., Ichiyama K., Nagashima S. (2009). ORF3 protein of hepatitis E virus is essential for virion release from infected cells. *J Gen Virol* ;**90**:1880e91.