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Dynamical behaviour of Norovirus: A Mathematical Approach

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Abstract: Norovirus is a RNA virus of the family *Caliciviridae*. It is the major cause of epidemic and sporadic gastroenteritis worldwide and responsible for substantial morbidity, mortality and healthcare costs. It can chronically infect immune compromised patients. The transmissibility and the enhancements of norovirus depends on several factors, including the small inoculum required to produce infection (100 viral particles), prolonged viral shedding, and its ability to survive in the environment.In this research article, a mathematical model of norovirus is proposed and analysed. Here a four dimensional mathematical model is considered. The dynamical behaviour of the system is studied analytically. Existence condition and stability analysis are performed. Our aim is to control the disease caused by norovirus by using control therapeutic approach.

Keywords: Caliciviridae, Gastroenteritis, Norwalk virus.

I. INTRODUCTION

Human norovirus which is previously known as Norwalk virus, was first identified in stool specimens which was collected during an outbreak of gastroenteritis in Norwalk, OH. And it was the first viral agent which caused gastroenteritis [1]. In 1929, first it was described as “winter vomiting disease” for its seasonal predilection and the frequent preponderance of patients with vomiting as a primary symptom [2]. Human noroviruses (HuNoVs) are a major cause of gastroenteritis outbreaks across the globe and childhood diarrhoea across the globe [3]. Characteristically HuNoV gastroenteritis is a severe illness. Also, chronic HuNoV infection presents a debilitating and often intractable problem to immune compromised persons [4]. Further, prolonged asymptomatic HuNoV infection and shedding may result spreading of the virus. Importantly, in animal models NoV infection can interact with allelic host genome variations to induce inflammatory bowel disease-like phenotypes which raises the possibility that NoV infection may last in the gut long after the resolution of an acute illness [5]. Gastroenteritis can be caused by a number of organisms, including many viruses and bacterial pathogens; however, viruses pose a particular problem owing to the limited number of antiviral therapies available for treatment [6].

The length of the viral genome is 7.4–7.7 kb and is organized into three or four open reading frames (ORFs). A large number of polyproteins is encoded by the 50 proximal ORF1. Polyproteinis cleaved by a virus-encoded protease (Pro; NS6) into at least six mature non-structural proteins including the viral RNA-dependent RNA polymerase (NS7; RdRp). NoVs have onlyone major structural protein, which is encoded by ORF2. This capsid protein which is referred to as VP1, is organized into a well conserved internal shell (S) domain and a protruding (P) domain formi dimeric VP1 arches and the P domain can be further subdivided into a P1 stalk subdomain and a hypervariable surface- exposed P2 subdomain that localizes to the tips of the arches [7]. A minor structural protein called VP2 is encoded by ORF3. A subgenomic RNA translates the two structural proteins VP1 and VP2. For MuNoVs, a fourth ORF overlaps over ORF2; translation from this alternative ORF4 produces a identified protein virulence factor 1 (VF1) [8, 9]. The 50 ends of NoV genomic and subgenomic RNAs are covalently linked to a small virus-encoded protein which is known as VPg, and the 30 ends are polyadenylated [10].

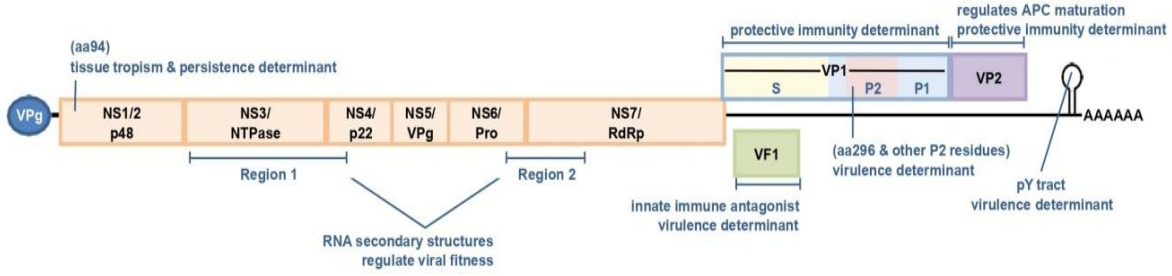

Fig 1: The human norovirus genome [10]

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Balb/c mice deficient in the recombination activating gene (RAG) and common gamma chain (gc) were ‘‘humanized with human stem cells CD34+ following irradiation. It was seen that mice were infected with filtered HuNoV-containing stool by combined peroral(p.o.) and intraperitoneal (i.p.) routes. Infection was detected with the measurement of increased genome titters over input by qRTPCR and viral protein expression by immunohistochemistry (IHC). Two VP1 positive Kupffer cells is shown by the image. (Middle)Balb/c RAG/gc-deficient mice were infected with HuNoV-containing stool filtrate by oral and/or intraperitoneal routes, and infection was measured above. Two NS6-positive cells in the spleen are shown by the image. No infection was seen in following oral infection. (Bottom) B6/B10 RAG/gc-deficient miceor wild-type (WT) Balb/c caused infection to the p.o.or i.p. routes, but no increases in viral genome-titters over input were detected, demonstrating that both the immune status and the genetic background are important susceptibility factors in this model[10].

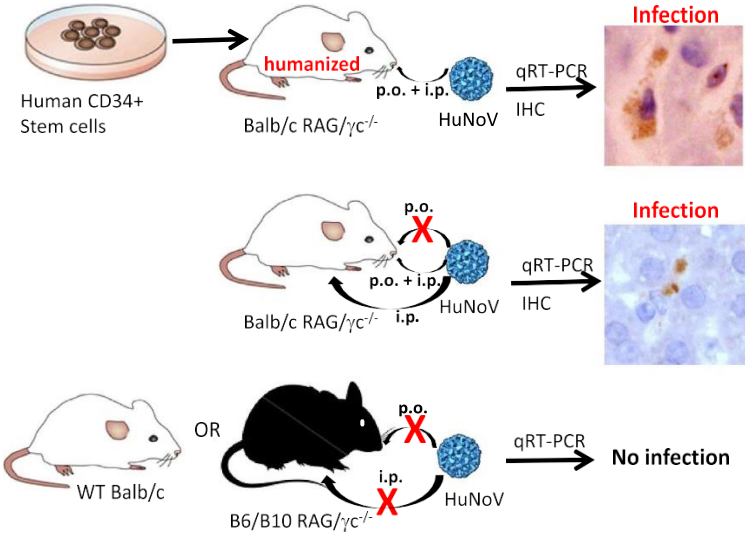

Fig 2: Human Norovirus Mouse Model [10]

The dominating symptoms of norovirus infection are vomiting and diarrhea and are generally of a relatively short duration. For example, in an analysis of 4 outbreaks over 3 years in an inpatient psychiatric unit in Taiwan that affected 172 patients and 7 health care workers [11], diarrhoea occurred in 87.5% and vomiting occurred in 25.5% of patients, while 4.4% complained of having abdominal pain and 2.2% had fever. The mean duration of symptoms was 2.1 -1.5 days, with a range of 1.2 to 2.8 days; 86.4% patients had symptom resolution within 1 to 3 days [12].

Several studies, with various degrees of evidence quality, on infection prevention and control practices to interrupt the transmission of norovirus in health care settings which have been summarized in the HICPAC (Healthcare Infection Control Practices Advisory Committee) guidelines for the prevention and control of norovirus gastroenteritis outbreaks. The three main strategic areas included staff and patient policy development, hand hygiene, and proper environmental disinfection [13,14].

II. DEVELOPMENT OF MATHEMATICAL MODEL

We consider that prey population is facing an infectious disease, where the predator feeds on both healthy and infected preys. Let S_h is the susceptible human population, I_h is the infected human population, E_h is the symptomatic human population, A_h is the asymptomatic human population, R_h is the recovered human population.

$$\frac{dS_h}{dt} = \lambda_h - \beta_h S_h I_h + \theta R_h$$

$$\frac{dE_h}{dt} = \beta_n S_h I_h - \alpha_h E_h - \mu_h E_h$$

$$\frac{dI_h}{dt} = \alpha_h E_h - v_h I_h - \mu_h I_h$$

$$\frac{dA_h}{dt} = v_h I_h - \mu_h A_h$$

$$\frac{dR_h}{dt} = \rho A_h - \theta R_h - \mu_h R_h$$

λ_h is the growth rate, β_h is the infection rate, μ_h is the death rate, θ is the recovered rate

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III. EXISTENCE AND LOCAL STABILITY ANALYSIS OF THE EQUILIBRIUM POINTS

There are 5 equilibrium points of the given system of equations and the points are $E_0(0,0,0,0,0)$, $E_1(\frac{\lambda_h}{\mu_h},0,0,0,0)$,
$E_2(S_H^2,E_h^2,I_h^2,0,0,0)$
where S_H^2,E_h^2,I_h^2 satisfy the equations
$\lambda_h-\beta_h S_h^2 I_h^2-\mu_h S_h^2=0$,
$\beta_h S_h^2 I_h^2-\alpha_h E_h^2-\mu_h E_h^2=0$,
$\alpha_h E_h^2-\nu_h I_h^2-\mu_h I_h^2=0$,
$E_3(S_h^3,E_h^3,I_h^3,A_h^3,0)$,

where $S_h^3, E_h^3, I_h^3, A_h^3$ satisfy the equation $\lambda_h-\mu_h(S_h^3+E_h^3+I_h^3+A_h^3)-\rho A_h^3=0$,
The interior point equilibrium is $E^*(S_h^*,E_h^*,I_h^*,A_h^*,R_h^*)$ where, $S_h^*,E_h^*,I_h^*,A_h^*,R_h^*$ satisfy the given system of equations

Lemma 1: The equilibrium point $E_0(0,0,0,0,0)$ is always stable.

Proof: All the Eigen values corresponding to the matrix are negative. Therefore the equilibrium point E_0 is stable.

Lemma 2: The point $E_1(\frac{\lambda_h}{\mu_h},0,0,0,0)$ is locally asymptotically stable if $(\alpha_h+2\mu_h+\nu_h)>0\&\{\alpha_h(\mu_h+\nu_h-\beta_h S_h)+\mu_h(\mu_h+\nu_h)\}>0$

Proof: The eigen values of the corresponding Jacobian matrix are $(-\mu_h),-(\rho+\mu_h),-(\theta+\mu_h)$, and the other two eigen values will have negative values iff $(\alpha_h+2\mu_h+\nu_h)>0\&\{\alpha_h(\mu_h+\nu_h-\beta_h S_h)+\mu_h(\mu_h+\nu_h)\}>0$.

So the equilibrium point E_1 is LAS if $(\alpha_h+2\mu_h+\nu_h)>0\&\{\alpha_h(\mu_h+\nu_h-\beta_h S_h)+\mu_h(\mu_h+\nu_h)\}>0$

Lemma 3: The equilibrium point $E_2(S_h^2,E_h^2,I_h^2,0,0)$ is locally asymptotically stable if the equation

$a_{11}>0$, $\begin{vmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{32} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ 0 & a_{32} & a_{32} & 0 \\ 0 & 0 & a_{43} & a_{44} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 & a_{15} \\ a_{21} & a_{22} & a_{23} & 0 & 0 \\ 0 & a_{32} & a_{32} & 0 & 0 \\ 0 & 0 & a_{43} & a_{44} & 0 \\ 0 & 0 & 0 & a_{54} & a_{55} \end{vmatrix}>0$,

and,
$\{(\beta_h S_h^2+\alpha_h+\nu_h+\rho+\theta+5\mu_h)(\beta_h I_h^2+\mu_h)\}>0$,

$\{10\mu_h^2+4\mu_h(\alpha_h+\nu_h+\rho+\theta+\beta_h I_h^2)+\alpha_h(\beta_h I_h^2+\nu_h+\rho-\beta_h S_h^2)+\beta_h I_h^2(\nu_h+\rho+\theta)+\rho(\nu_h+2\theta)\}>0$,

$(-a_{11})[a_{22}(a_{33}+a_{44}+a_{55})+a_{33}(a_{44}+a_{55})+a_{44}a_{55}-a_{23}.a_{32}]-a_{44}[a_{22}(a_{33}+a_{55})-a_{23}.a_{32}]+a_{55}(a_{23}.a_{32}-a_{22}.a_{33})>0$,

$-a_{11}[a_{44}(-a_{22}a_{33}-a_{22}a_{55}-a_{55}a_{33}+a_{23}a_{32})+a_{55}(-a_{22}a_{33}+a_{23}a_{32})]+a_{44}a_{55}(a_{22}a_{33}-a_{23}a_{32})-a_{13}a_{32}a_{21}(a_{44}+a_{55})>0$,

$(a_{11}a_{44}a_{55})(a_{23}.a_{32}-a_{22}.a_{33})-(a_{21}a_{32})(a_{13}a_{44}a_{55}+a_{43}a_{15}a_{54})>0$

Where, $a_{11}=-\beta_h I_h^2-\mu_h$, $a_{13}=-\beta_h S_h^2$, $a_{15}=\theta$, $a_{21}=\beta_h I_h^2$, $a_{22}=-\alpha_h-\mu_h$, $a_{23}=\beta_h S_h^2$

$a_{32}=\alpha_h$, $a_{33}=-\nu_h-\mu_h$, $a_{43}=\nu_h$, $a_{44}=-\rho-\mu_h$, $a_{54}=\rho$, $a_{55}=-\theta-\mu_h$

Lemma 4: The equilibrium point $E_2(S_h^3,E_h^3,I_h^3,A_h^3,0)$is locally asymptotically stable if

$a_{11}>0$, $\begin{vmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{32} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ 0 & a_{32} & a_{32} & 0 \\ 0 & 0 & a_{43} & a_{44} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 & a_{15} \\ a_{21} & a_{22} & a_{23} & 0 & 0 \\ 0 & a_{32} & a_{32} & 0 & 0 \\ 0 & 0 & a_{43} & a_{44} & 0 \\ 0 & 0 & 0 & a_{54} & a_{55} \end{vmatrix}>0$,

and
$\{10\mu_h^2+4\mu_h(\alpha_h+\nu_h+\rho+\theta+\beta_h I_h^3)+\alpha_h(\beta_h I_h^3+\nu_h+\rho-\beta_h S_h^3)+\beta_h I_h^3(\nu_h+\rho+\theta)+\rho(\nu_h+2\theta)\}>0$,

$(-a_{11})[a_{22}(a_{33}+a_{44}+a_{55})+a_{33}(a_{44}+a_{55})+a_{44}a_{55}-a_{23}.a_{32}]-a_{44}[a_{22}(a_{33}+a_{55})-a_{23}.a_{32}]+a_{55}(a_{23}.a_{32}-a_{22}.a_{33})>0$,

$(-a_{11})[a_{44}(-a_{22}.a_{33}-a_{22}.a_{55}-a_{33}.a_{55}+a_{23}.a_{32})+a_{55}(a_{23}.a_{32}-a_{22}.a_{33})]+(a_{44}a_{55})(a_{23}.a_{32}-a_{22}.a_{33})-(a_{13}a_{21}a_{32})(a_{44}+a_{55})>0$,

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$(a_{11} a_{44} a_{55})(a_{23}.a_{32}- a_{22.} a_{33})-(a_{21}a_{32})(a_{13} a_{44} a_{55}+a_{43} a_{15} a_{54}) >0.$

Where, $a_{11} =-\beta_h I_h^3 - \mu_h$, $a_{13} = -\beta_h S_h^3$, $a_{15} = \theta$, $a_{21} = \beta_h I_h^3$, $a_{22} = -\alpha_h - \mu_h$, $a_{23} = \beta_h S_h^3$
$a_{32} = \alpha_h$, $a_{33} = -\nu_h - \mu_h$, $a_{43} = \nu_h$, $a_{44} = -\rho - \mu_h$, $a_{54} = \rho$, $a_{55} = -\theta - \mu_h$

Lemma 5: The interior point $E^*(S_h^*, E_h^*, I_h^*, A_h^*, R_h^*)$is locally asymptotically stable if

$a_{11}>0$, $\begin{vmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 0 & a_{32} & a_{32} \end{vmatrix} > 0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ 0 & a_{32} & a_{32} & 0 \\ 0 & 0 & a_{43} & a_{44} \end{vmatrix}>0$, $\begin{vmatrix} a_{11} & 0 & a_{13} & 0 & a_{15} \\ a_{21} & a_{22} & a_{23} & 0 & 0 \\ 0 & a_{32} & a_{32} & 0 & 0 \\ 0 & 0 & a_{43} & a_{44} & 0 \\ 0 & 0 & 0 & a_{54} & a_{55} \end{vmatrix}>0$

and

$A^* = \{(\beta_h S_h^* + \alpha_h + \nu_h + \rho + \theta + 5\mu_h)(-\beta_h I_h^* - \mu_h)\} > 0,$
$B^* =\{10+4\mu_h(\alpha_h + \nu_h + \rho + \theta + \beta_h I_h^*) + \alpha_h(\beta_h I_h^* + \nu_h + \rho - \beta_h S_h^*) + \beta_h I_h^*(\nu_h + \rho + \theta) + \rho(\nu_h + 2\theta)\}$ >0 , C^* =(-$a_{11})[a_{22}(a_{33}+a_{44}+a_{55})+ a_{33}(a_{44}+a_{55})+ a_{44} a_{55}-a_{23}.a_{32}]- a_{44}[a_{22}(a_{33}+a_{55})- a_{23}.a_{32}]+ a_{55}(a_{23}.a_{32}- a_{22.} a_{33}) >0,$
$D^* =(-a_{11})[a_{44}(-a_{22}.a_{33}-a_{22}.a_{55}-a_{33}.a_{55}+a_{23}.a_{32})+a_{55} (a_{23}.a_{32}- a_{22.} a_{33})]+(a_{44} a_{55})(a_{23}.a_{32}- a_{22.} a_{33})-(a_{13}a_{21}a_{32})(a_{44}+a_{55}) >0,$
$E^*=(a_{11} a_{44} a_{55})(a_{23}.a_{32}- a_{22.} a_{33})-(a_{21}a_{32})(a_{13} a_{44} a_{55}+a_{43} a_{15} a_{5.}$

Where, $a_{11} =-\beta_h I_h^* - \mu_h a_{13} = -\beta_h S_h^*$, $a_{15} = \theta$, $a_{21} = \beta_h I_h^*$, $a_{22} = -\alpha_h - \mu_h$, $a_{23} = \beta_h S_h^*$, $a_{32} = \alpha_h$, $a_{33} = -\nu_h - \mu_h$, $a_{43} = \nu_h$, $a_{44} = -\rho - \mu_h$, $a_{54} = \rho$, $a_{55} = -\theta - \mu_h$.

IV. CONCLUSION

Norovirus is an acute cause of morbidity due to severe gastroenteritis both within health care institutions and in the broader community. Although mortality is generally limited to the extremes of age, the disease exacts a significant toll on the health care system.

The treatment for norovirus gastroenteritis is same as other diarrheal illnesses, i.e.oral rehydration with fluids and electrolytes if the patient is alert and able to drink, or intravenous fluidscan be usedif vomiting and dehydration are severe. Antimotility and antisecretory agents can be useful in adults to decrease diarrhoea in situations when a person's performance is critical.

Here in this research article we propose a deterministic mathematical model of norovirus infection. It was shown that the model is mathematically and epidemiologically well posed. We observed the existence condition and the stability condition of the several equilibrium points of the given system

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