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Mathematical modelling of hepatitis C treatment for injecting drug users

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ABSTRACT

Hepatitis C virus (HCV) is a blood-borne infection that can lead to progressive liver failure, cirrhosis, hepatocellular carcinoma and death. In developed countries, the majority of HCV infections are transmitted via injecting drug users (IDUs). Despite effective antiviral treatment for HCV, very few active IDUs are treated. Reluctance to treat is partially due to the risk of reinfection. We develop a mathematical model of HCV transmission amongst active IDUs, and examine the potential effect of antiviral treatment. As most mathematical models of interventions utilise a treatment function proportional to the infected population, but many policy implementations set fixed yearly targets for specific numbers treated, we study the effects of using two different treatment terms: annually treating a proportion of infecteds or a fixed number of infecteds. We examine the behaviour of the two treatment models and find different bifurcation behaviours in each case. We calculate analytical solutions for the treatment level needed for disease clearance or control, and observe that achievable levels of treatment can result in control or eradication across a wide range of prevalence levels. Finally, we calculate the sensitivity of the critical treatment threshold to the model parameters, and find that for a given observed prevalence, the injecting duration and infection risk play the most important role in determining the treatment level needed. By contrast, the sensitivity analysis indicates the presence (or absence) of immunity does not alter the treatment threshold. We conclude by discussing the public health implications of this work, and comment on the importance and feasibility of utilising treatment as prevention for HCV spread amongst IDUs.

1. Introduction

Hepatitis C virus (HCV) is a blood-borne disease with an estimated global prevalence of 2–3%, or 130–170 million people, and is one of the leading causes of chronic liver disease (Shepard et al., 2005). If left untreated, about 7–18% of those infected will progress to liver disease within 20 years, which can result in progressive liver failure, cirrhosis, hepatocellular carcinoma and death (Seeff, 2009).

In developed countries, the primary mode of transmission is amongst injecting drug users (IDUs) through needle and syringe sharing, with over 80% of new cases in the UK attributed to injecting drugs (ACMD, 2009). HCV is easily transmitted amongst IDUs, with 15–90% of IDUs testing positive for HCV antibodies (Page-Shafer et al., 2008; Judd et al., 2005; Hahn et al., 2002). Current preventative measures to reduce HCV transmission such as health education and advice, needle and syringe exchange, and opiate substitution therapy aim to prevent transmission by reducing unsafe injecting (ACMD, 2009). However, public health surveillance indicates substantial decreases in prevalence have not been achieved (Palmateer et al., 2010).

HCV antiviral treatment (peginterferon-α and ribavirin) is effective, resulting in viral clearance in 45–80% of cases, depending on HCV genotype (NICE, 2000). Prior to 2002, guidelines in the US and UK recommended against treating active IDUs. However, current guidelines now do not exclude IDUs from treatment eligibility, given mounting evidence that IDUs exhibit a similar response to treatment, and are just as compliant with treatment as ex- or non-IDUs (Hellard et al., 2009; NICE, 2006; Shepherd et al., 2007; NIH, 2002). Nevertheless, despite these recommendations and the high numbers of IDUs infected, very few ($<3-4\%$) active IDUs have ever been treated (Grebely et al., 2006; Seal et al., 2005). Studies on treatment barriers have indicated a reluctance to treat active IDUs due to the possibility of subsequent reinfection (Booth et al., 2001; Reimer et al., 2005; Foster, 2008).

We examine the potential of antiviral treatment as a prevention strategy for HCV amongst IDUs. By using antiviral treatment to reduce prevalence amongst active IDUs, the treatment can act to reduce the risk of infection for other IDUs. But to what extent? This paper examines the potential impact of HCV treatment on prevalence

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and transmission, including the possibility of reinfection. We incorporate two treatment scenarios (treating a proportion of infected IDUs, and a fixed number of IDUs) and examine the resulting dynamics and treatment needed for eradication. Treating a constant proportion of the population is the function most commonly used in infectious disease modelling. However, annually treating a fixed number of IDUs would be more likely in the initial stages of a treatment delivery programme, or in situations with budget constraints. Hence, we analyse both situations.

2. Background and assumptions for the model

Infection with HCV leads to a brief acute stage, which is relatively short (on the order of weeks to months) in comparison to the prolonged chronic stage (on the order of decades) (ECMDDA, 2004). In the first few weeks, viral levels may be undetectable, increasing but possibly remaining low during the remainder of the acute stage. A fraction of people (about 26%) spontaneously clear the acute infection (Micallef et al., 2006). The specifics of spontaneous clearance are not well known, although women and young adults exhibit higher spontaneous recovery rates. Due to the relatively short duration of the acute stage and the small fraction who spontaneously clear, we neglect the small contribution towards infections from the acute IDUs who spontaneously clear. Those who spontaneously clear either become susceptible again, or may become immune. The concept of sterilising immunity following exposure to HCV is uncertain. We assume a low proportion become immune, and explore the sensitivity of the model with respect to immunity in the sensitivity analysis. The remaining fraction which do not spontaneously clear the acute infection progress to the chronic infection stage.

There are six identified HCV genotypes (numbered 1–6), with different distributions among geographically distinct IDU populations. In the UK, for example, genotype 1 comprises about 50% and genotypes 2 and 3 together comprise about 50% (NICE, 2006). In the US, the proportion of genotype 1 is slightly higher (about 70%). The differences in disease progression between the genotypes is not yet clear, but they do show differences in response rates to therapy, with genotypes 2 and 3 exhibiting higher cure rates than genotype 1. Treatment with peginterferon and ribavirin results in a sustained viral response 6 months after treatment in 40–50% of people with genotype 1, and 75–85% with genotype 2 or 3 (NICE, 2006). In this model, we do not explicitly model infections with different genotypes, and instead track total infections and use a weighted average cure rate. Additionally, we examine a worst-case scenario with a population comprised entirely of the harder to treat genotype 1, in case the differential treatment success rates result in a population shift of the genotype distribution. Further, countries such as the United States have a higher proportion of genotype 1 and so would tends towards these scenarios (Klevens et al., 2010).

Antiviral treatment leads to a substantial reduction in viral load in the first few weeks (even among some eventual nonresponders). Hence, we assume that IDUs currently on treatment are non-infectious. Due to the lack of evidence to suggest otherwise, we assume that the chances of spontaneous clearance and immunity are equal for naive and re-infected IDUs. Furthermore, we assume that the probability of treatment success is the same between naive and re-infecteds, which is supported by experimental evidence (Litwin et al., 2009). Most importantly, we assume that people who fail treatment (and return to the chronically infected pool) can be retreated with the same chance of success. This assumption is based on the recent data showing that novel drugs (specifically Teleprevir) may have high success rates (50%) amongst nonresponders with genotype 1, and the anticipation that other future drugs will have similar effects (McHutchison et al., 2009).

3. Details and explanation of the model

We use a system of ordinary differential equations to describe the transmission of HCV amongst active IDUs. We utilise a four compartment model, tracking susceptible, chronically infected, treated, and immune IDUs. Susceptible IDUs become infected through sharing of needles with an infected IDU. About one quarter spontaneously clear the infection, and become susceptible or immune. The remaining three-quarters progress to chronic infection. Chronic infecteds can be treated, with a certain chance of success, and either fail treatment and return to the infection compartment, or clear the disease and become susceptible again or immune.

In our model, X denotes susceptible IDUs (including those who have cleared the infection), C denotes both chronically infected and acutely infected IDUs which will proceed to chronic infection, T denotes IDUs in treatment, Z denoting immune IDUs, τ is time in years, and where N=total population=$X+Z+C+T$. The equations describing the HCV transmission are:

$$\frac{dX}{d\tau} = \theta - \pi(1-\delta+\delta\xi)\frac{C}{N}X + \omega\alpha\sigma T - \mu X, \tag{1}$$

$$\frac{dC}{d\tau} = \pi(1-\delta)\frac{C}{N}X - f(C) + \omega(1-\alpha)T - \mu C, \tag{2}$$

$$\frac{dT}{d\tau} = f(C) - \omega T - \mu T, \tag{3}$$

$$\frac{dZ}{d\tau} = \pi\delta\xi\frac{C}{N}X + \omega\alpha(1-\sigma)T - \mu Z, \tag{4}$$

with initial conditions $X(0)=X_0$, $C(0)=C_0$, $T(0)=0$, and $Z(0)=0$.

Eq. (1) represents the susceptible population, where new IDUs enter at a fixed rate θ. The second term in Eq. (1) models the infection of a susceptible IDU, which is proportional to the number of susceptibles, the fraction of the population chronically infected, and the infection rate, π. The acute infection spontaneously clears in a proportion δ, a fraction of which become immune at a proportion ξ. The remaining infected fraction which do not spontaneously clear, $1-\delta$, progress to chronic infection. The third term in Eq. (1) represents IDUs who exit treatment at a rate ω, with successful treatment proportion α, and who are the part of the proportion not immune, σ. Due to the short duration of the acute stage, the number of infections caused by people with acute HCV who spontaneously clear or become immune is small, and we neglect it for model simplicity.

In each of the Eqs. (1)–(4), IDUs leave (due to death or ceasing injection) proportional to the rate μ.

Eq. (2) models chronically infected IDUs. The first term represents those who enter from the susceptible pool, which is proportional to the number of susceptibles, the fraction of the population chronically infected, the infection rate, π, and the fraction who do not spontaneously clear the acute infection $1-\delta$. The fraction of nonresponders to treatment, $1-\alpha$, return from treatment proportional to rate ω.

The second term in Eq. (2), $f(C)$, represents the movement of infected IDUs into treatment. In this paper, we examine two forms of the treatment recruitment function, which we describe in Section 3.1.

Eq. (3) represents IDUs currently in treatment. Infected IDUs enter treatment at the rate $f(C)$ as discussed in Eq. (2). Due to the reduction of viral loads during treatment, we assume that IDUs on