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Developing and Implementing Models for the Prevalence, Incidence and Geographic Spread of Opiate Use in Ireland.
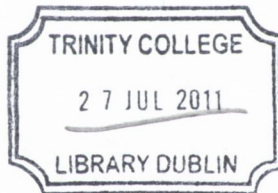
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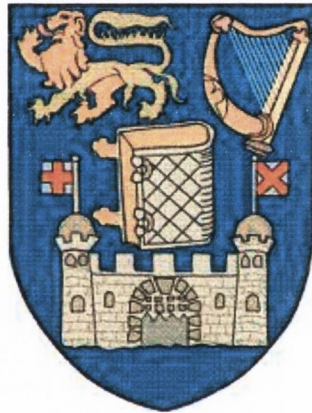
Supervisor: Prof. Catherine Comiskey

School of Nursing and Midwifery,
Faculty of Health Sciences

A thesis submitted to the
University of Dublin, Trinity College
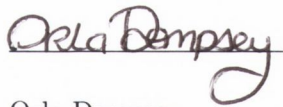for the degree of
Doctor of Philosophy

February 17, 2011

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Summary

The objective of this study is to further develop and implement established mathematical models for the first time to the problem of estimating the true size of the opiate epidemic and to develop and apply existing mathematical models to the problem of modelling the geographic spread of opiate use in Ireland. Estimates of the true size and spread of the opiate epidemic are difficult to obtain due to the hidden nature of opiate use however these estimates are vital for policy makers and service providers when planning for the provision of effective treatment services. In a bid to estimate the true size of the epidemic this research focuses on deriving suitable models to estimate the prevalence and incidence of opiate use in Ireland.

The back calculation model from AIDS epidemiology is applied to the problem of estimating the hidden, untreated incidence of opiate use. An estimate of the hidden incidence is produced by back calculating from the known treated incidence through an estimated latency period of opiate use. The back calculation model is analytically solved and the solutions obtained are used to produce estimates of the hidden, untreated incidence of opiate use when the exact rate of progression to treatment is unknown. In a bid to produce more accurate incidence estimates data on times from first opiate use to first treatment are obtained.

A model for the exact rate of progression to first treatment is determined through

fitting Gamma and Weibull probability distributions to data on 5,022 times to treatment for previously untreated opiate users. The exact rate of progression to first treatment along with a range of forms of treated incidence is applied to the back calculation model which is then solved analytically for the first time. The solutions obtained are applied to the problem of estimating the true size of the hidden, untreated population of opiate users who will present for their first treatment in the future.

A vast array of techniques to estimate the prevalence of drug and opiate use exist however a new approach which is not heavily data dependent would be beneficial to researchers, policy makers and service providers. An integral equation model to estimate the prevalence of opiate use is derived. The prevalence model derived is based on the models developed for the hidden incidence of opiate use. Estimates of the prevalence of opiate use are produced when the exact rate of progression to treatment is unknown and known. Whilst estimates of the true size of the epidemic are necessary, it is essential to determine where the epidemic will spread in order to determine measures to prevent further spread. A partial differential equation which uses the prevalence estimates produced, is derived to describe the geographic spread of opiate use in Ireland. Techniques to estimate model parameters for the partial differential equation are developed and the hypothetical geographic spread of opiate use from Dublin to Wexford is simulated.

Models for the prevalence, incidence and geographic spread of opiate use have been developed. The models derived are not heavily data dependent and could be utilised to produce estimates of any problematic drug use in any specified location providing the necessary data is available.

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Acknowledgments

Firstly I would like to take this opportunity to thank my supervisor, Prof. Catherine Comiskey. Her support, encouragement, and time throughout the course of my Ph.D. are much appreciated. The enthusiasm she has for her research was motivational at times when the Ph.D. process was difficult.

Many thanks to Dr. Conor Houghton for his advice on C++ and to Dr. Catherine Hurley for sharing her expertise on the statistical package Minitab. I am grateful to Dr. Emma White for her words of wisdom and for sharing details of her experience in pursuit of her Ph.D. Thanks to my colleagues and friends at the School of Nursing and Midwifery, Trinity College Dublin, particularly Emma and Anne for interesting discussion!!

A special mention must be given to my family and friends. Thanks to my parents, sisters and niece for their support and encouragement in all my pursuits (and to mam and dad for the cups of tea and dinners as I was finishing this). Finally to my husband Gary, without his patience, encouragement and constant reminders that I was almost there I could not have done this, thank you so much. Thanks to

my friends for their support!

Chapter 1

Introduction to Mathematical Modelling and Problem Drug Use

1.1 Thesis Introduction and Aims

The misery and suffering caused by infectious diseases is incalculable and presents significant challenges to experts in several branches of science, research and public health service (Bailey 1975). Mathematical models have been developed and new applications of existing models in relation to numerous communicable diseases have been established to enable these experts to deal with the challenges they face. Mathematical modelling has been developed and applied to a broad range of problems in biology and population studies, such as modelling the prevalence and incidence of disease, modelling the latent and incubation periods of infections, measuring mortality rates and describing the geographic spread of disease, to name but a few. Mathematical and statistical modelling are crucial in the modelling of clinical trial data for new vaccines such as the Human papillomavirus infection (HPV) vaccine in the United Kingdom and Australia. These models have given experts insight into the usefulness and cost effectiveness of rolling out these new vaccines and have enabled health service providers and funding agencies to allocate increasingly scarce

resources.

According to Bailey (1975) understanding the nature of epidemic processes assists the prevention of infectious disease. Brauer (2009) acknowledges that the following questions would be of interest to public health physicians when faced with an epidemic:

- How severe will the epidemic be?

- How many individuals will be affected and require treatment?

- What is the maximum number of individuals that will require treatment at any time?

This is also true of the drug use epidemic, if epidemiologists, health care providers and those responsible for resource allocation have an understanding of the nature of the drug use epidemic, more informed decisions regarding prevention and intervention could be made. Thus the objective of this study is to further develop and apply established mathematical techniques for the first time to the problem of estimating the prevalence and incidence of opiate use and to develop and implement existing mathematical models to the very real and longstanding problem of modelling the geographical spread of opiate use.

1.1.1 Thesis Outline

This chapter outlines the history and applications of mathematical modelling in relation to infectious disease to date. It also gives an overview of the history of drug use particularly opiate use and drug policies in Ireland. Following on from the history of mathematical modelling and drug use, the history of mathematical

modelling in relation to drug use is outlined. The specific aim of this chapter is to outline the history of the existing mathematical techniques used in modelling epidemics and to provide a background to the opiate epidemic in the Irish setting. In order to fulfill this aim we look at:

- The modelling process and what an appropriate model must include.

- How mathematical modelling in epidemiology has evolved in an effort to provide a general understanding of existing techniques which may be applied to the problem of estimating the size of the opiate epidemic in Ireland.

- Models used in AIDS epidemiology, particularly integral equations, due to the well documented association between AIDS and opiate use.

- The background to illicit drug use, specifically opiate use and drug policy in the Irish setting, in order to establish how patterns of drug use have evolved to date.

- Mathematical models which have previously been applied to substance misuse.

Chapter 2 introduces the back calculation method as an estimation technique for the *incidence* of untreated opiate use in Ireland. In Chapter 2 basic *incidence* estimates of illegal opiate use are produced, using published incubation period data and data on the number of new first treatment cases for illegal opiate use over a period of time in Ireland. This published incubation data sets the stage for Chapter 3 where probability distribution models are introduced as a technique for modelling the rates at which opiate users in Ireland progress to first treatment. These incubation period distribution models, in combination with the back calculation technique

introduced in earlier chapters, are implemented to produce more refined *incidence* estimates in Chapter 4. In Chapter 5 integral equations are applied to the problem of estimating the *prevalence* of untreated opiate use in Ireland. Chapter 6 looks at developing and implementing differential equations for describing the geographic spread of illegal opiate use in a population as a function of time. Numerical simulations are then performed using parameters estimated from Irish data. Chapter 7 summarises the research conducted in this study with conclusions and suggestions of future work.

1.2   The Modelling Process

A mathematical model is defined as a simplification of a real world problem in the form of mathematical equations and Barnes & Fulford (2002) describe the stages of the construction of a mathematical model as a cyclic process, which is illustrated in Figure 1.1.
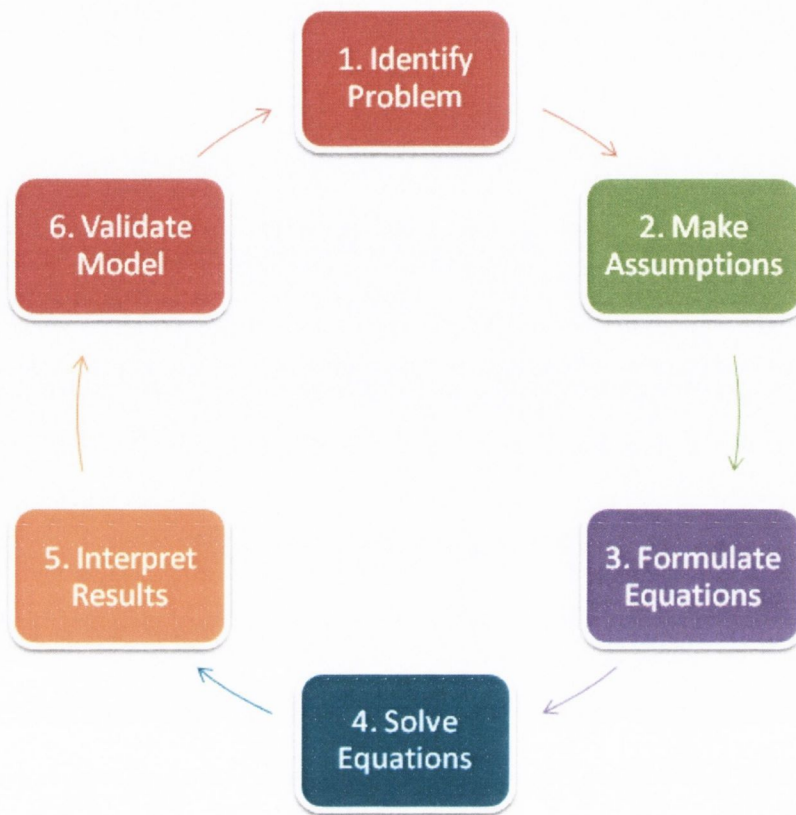
Figure 1.1: Schematic diagram of the modelling process. Source: Barnes & Fulford (2002, p. 10).

A useful and appropriate mathematical model must:

- Include the main features of the phenomena it describes.

- Be simple for the purpose of analysis and application to the real world problem it describes.

The starting point in constructing a mathematical model is to review the literature for existing models and draw on knowledge of those existing models. In the next section, the starting point for this research, a brief introduction to the history of mathematical modelling in epidemiology, is given.

1.3 Introduction to Mathematical Modelling in Epidemiology

Mathematical and statistical modelling of epidemics has a long and extensive history with modelling in population biology dating at least as far back as the 17th century. Modellers in the past have focused their research on modelling the spread of epidemics such as measles, malaria, Tuberculosis (TB), Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) and Severe Acute Respiratory Syndrome (SARS) (Kermack & Mc Kendrick 1927, Ross 1911, Bailey 1975, Anderson & May 1991, Murray 2003b, Department of Health and Social Security 1988).

The first records of epidemic outbreaks can be dated back at least as far as ancient Greeks with Epidemics of Hippocrates (459-377 B.C.)(Bailey 1975). Mathematical and statistical models originated in early medical statistics when Graunt and Petty first studied the London Bills of Mortality in the 17th century. Bailey noted that progress was slow and the next record of mathematical modelling in relation to disease was in the 18th century (Bailey 1975). In 1766, the mathematician Daniel Bernoulli used a mathematical method to evaluate the effectiveness of the variolation technique in a bid to produce immunity to the small pox disease. This was followed by Snow's study on the temporal and spatial pattern of cholera cases which enabled him to demonstrate that the disease was spread by the contamination of water supplies (Snow 1855).

One of the early mathematical techniques considered when modelling epidemics was an empirical approach which was the curve fitting process. Curve fitting involved constructing a curve or mathematical function which best fit a series of data points

and then using the fitted curve to predict future outcomes or to predict outcomes where data was unavailable. Farr (1840), as cited by (Bailey 1975) applied curve fitting techniques to data on small pox related deaths and later attempted to use a similar method to predict the course of an outbreak of rinderpest, also known as cattle plague, amongst cattle. Brownlee went on to conduct more in-depth studies of curve fitting to epidemic data, fitting various Pearsons curves to a wide range of diseases (Bailey 1975). Barnes & Fulford (2002) described empirical models as one of the most basic modelling techniques, however they discuss a lack of confidence in the applicability of the fitted curve outside the range of the data as a limitation of this kind of model.

According to Bailey, by the 1900's the growing availability of mortality statistics illustrated the problems facing public health authorities and more suitable models for more exact mathematical investigation were suggested due to breakthroughs in bacteriology. Perhaps this explains why early developments in mathematical modelling of infectious disease and the groundwork of the approach to epidemiology, based on compartmental models were made by public health physicians such as Sir Ross, R.A., W.H. Hamer, A.G. Mc Kendrick and W.O. Kermack between 1900 and 1935 (Brauer 2009).

Originally the vast majority of work on communicable diseases was deterministic in character. Deterministic models have no randomness involved in the future development of future states of the system and therefore produce the same output for a given starting condition. In 1906, Hamer introduced the 'mass action principle', the basis of all deterministic theories when he considered that the course of an epidemic depends on the rate of contact between susceptible and infectious individuals. Ross

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worked on formulating a mathematical model for the diffusion of malaria. He used a continuous-time framework of the 'mass action principle' in his work on the dynamics of malaria in 1908 (Ross 1911). In 1902 Ross was awarded the Nobel Prize in medicine and was knighted in 1911 for his ground breaking work on the transmission of malaria. The concepts of birth rates, death rates, attack rates and recovery rates were introduced to deterministic models by Ross in 1911.

Kermack and Mc Kendrick formulated a simple compartmental model which was useful in predicting the behavior of outbreaks in their paper, "Contributions to the Mathematical Theory of Epidemics", which was published in 1927 (Brauer & Castillo-Chavez 2001). A compartmental or deterministic model involves assigning individuals in a population to different compartments which represent different stages of an epidemic. Kermack and Mc Kendrick produced a model with three compartments, $S(t)$, $I(t)$ and $R(t)$, is illustrated as;

$$\boxed{\text{Susceptibles, S(t)}} \longrightarrow \boxed{\text{Infected, I(t)}} \longrightarrow \boxed{\text{Recovered, R(t)}}$$
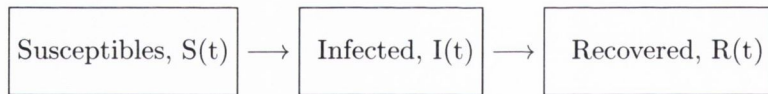
where;

- $S(t)$ is the number of individuals susceptible to a disease, in a population at time t.

- $I(t)$ is the number of infected individuals capable of transmitting the disease at time t to those individuals in the susceptible sub-group.

- $R(t)$ is the number of individuals who have been infected, have since recovered and can no longer become infected with the disease themselves or spread the infection at time t.

Throughout the history of mathematical epidemiology one of the most significant contributions was Kermack and Mc Kendrick's Threshold Theorem. The Threshold Theorem states that the introduction of infectious cases into a community of susceptibles would not result in an epidemic outbreak if the density of susceptibles was below a certain critical value. Soper (1929) carried out more deterministic work focusing on measles, using difference equations which were very similar to the differential equations of other researchers.

One of the first stochastic models, published by Mc Kendrick was a "continuous-infection" model (Bailey 1975), which involved an individual being infectious from the moment of infection until recovery, isolation or death. Stochastic models were considered as they take account of the probability aspects of a process. The nature and progression of diseases vary, particularly for new strains of diseases, therefore models for the future evolution of disease were described using probability distributions. The probability distribution models which accounted for the variable nature of disease progression were considered to provide a more realistic illustration of epidemics. Despite Mc Kendrick's work on the "continuous-infection" model it wasn't until the early 1940's that developments in the more complex stochastic processes were considered when modelling infectious diseases.

Whilst work continued on extending deterministic processes in the 1940's it was at this time that some of the most significant developments were made in the mathematical handling of stochastic processes. Some of the first work on stochastic disease models was published by Bartlett (1956). Bartlett was responsible for developing a partial differential equation model for the probability generating function of two variables, the susceptibles and the infectious (Bailey 1975). Bartlett demonstrated

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that a more realistic picture of a recurrent epidemic could be achieved by adopting a stochastic process. By the mid 1980's many deterministic and stochastic models to describe the immune system and its interaction with HIV existed (Murray 2003a).

Prior to 1957 a review of the history of mathematical epidemiology was non-existent until the first edition of Baileys classic text, "The Mathematical Theory of Infectious Diseases and its Applications" was published (Bailey 1975). At the time there were approximately 100 references to mathematical work in the literature and that had increased to 200 when Dietz published the review paper, "Epidemics and Rumours: A Survey" in 1967 Bailey (1975). Bailey states there was approximately 500 references when the second and final edition of "The Mathematical Theory of Infectious Diseases and its Applications" was published in 1975 further illustrating the growing trend in literature concerned with mathematical epidemiology. The text "Infectious Diseases of Humans" was published by Anderson & May (1991) with the primary aim of illustrating how simple mathematical models could be used to interpret observed trends in epidemiology. The text "Mathematical Epidemiology of Infectious Diseases" which covers both stochastic and deterministic modelling, was published by Diekmann & Heesterbeek (2000).

After reviewing some of the existing literature on the history of mathematical modelling in epidemiology, armed with an awareness of the different types of models used, the literature was examined with a view to drawing on previous researchers' tried and tested work in a bid to derive or develop and implement mathematical models for problem drug use, specifically opiate use. It was decided that mathematical models used in epidemiology could be developed and implemented when modelling opiate use as there are similarities in the characteristics of infectious disease and

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opiate use.

Individuals are initiated to opiate use through contact with other opiate users, this is similar to the transmission of some infectious diseases, such as bacterial meningitis, influenza, tuberculosis, impetigo and syphilis, which are all spread through contact with infected individuals. Mossong *et al.* (2008) found that the mixing pattern and contact characteristics of an individual were relevant to the spread of an infectious disease. Similarly, Cauilkins (2001) describes a "social contagion" model of recruitment to drug use, whereby friends who are current drug users initiate friends to drug use.

A trait which is common to some infectious diseases and opiate use is the hidden nature of both. Many individuals infected with a disease particularly sexually transmitted diseases like chlamydia, human papillomavirus and HIV are unaware they are infected with the disease as they remain asymptomatic for a long time (Eng & Butler 1997). As opiate use is an illegal activity an opiate user remains "hidden" from initiation to opiate use until presenting for first treatment or coming to the attention of authorities for drug related offences.

Another similar characteristic of infectious disease and opiate use is the variability in how people are affected by both. An infectious disease and opiate use can affect individuals differently depending on underlying factors such as health. There can be variation in the incubation period and progression of a disease depending on dose of inoculum and route of inoculation (Nelson & Masters Williams 2007). Similarly, the incubation period and progression of the opiate using career can vary for each individual. Finally there is an association between illicit drug use and some infectious diseases, as illegal drug use can lead to risky behavior such as needle

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sharing and unsafe sexual practices.

The following section gives a brief outline of integral equations and introduces integral equation models from infectious disease epidemiology which could be applied to modelling the prevalence, incidence and geographical spread of opiate use.

1.4   Models

Integral equations have previously been used in epidemiology to model infectious diseases such as AIDS, Tuberculosis and smallpox (Isham 1989, Salpeter & Salpeter 1998, Aldis & Roberts 2005). Integral equation models are of interest for this research due to their extensive use in AIDS epidemiology. Models from AIDS epidemiology are considered to model and estimate the true size of the opiate epidemic. The association between AIDS and injecting drug use is well documented. According to the United Nations Office on Drugs and Crime (2007) injecting drug users, particularly opiate users are at risk of contracting infectious diseases such as HIV/AIDS. A similarity of opiate use and the HIV infection is the hidden nature of both. Opiate use is a hidden activity from onset of use until treatment is requested, similarly HIV is hidden from initial infection until AIDS diagnosis is reported. An integral equation model from AIDS epidemiology which is the foundation model for this research on estimating the true size of the opiate epidemic is the back calculation model.

The Romanian mathematician Traian Lalescu (1882-1929) famous for his work on integral equations earned his Ph.D. in Mathematics from the University of Paris in 1908. Lalescu published the first book ever on the subject of integral equations, "Introduction to the Theory of Integral Equations" in 1911.

Integral equations are equations in which the unknown function $u(x)$ appears

under an integral sign, an example of a general integral equation in $u(x)$ is

$$u(x) = f(x) + \int K(x,t)u(t)\,\mathrm{d}t,$$

where $K(x,t)$ is the kernel of the integral equation which is a function of two variables. According to Anselone & Nashed (1988) integral equations can be broadly classified into the following categories;

- Integrodifferential equations which contain both derivatives and integrals of an unknown function.

- Integral transforms which map an equation from its original domain into another target domain which is easier to manipulate and solve than the original equation. The solution is then mapped back to the original domain with the inverse of the integral transform.

- Stochastic integral equations are integral equations in which one or more of the terms is a stochastic process.

- Singular integral equations are integral equations that have a singular kernel within the range of integration or if one or both of the limits of integration are infinite.

- Volterra integral equations are integral equations which have one variable limit of integration. These equations have previously used in demography.

- Fredholm integral equations are integral equations which have fixed limits of integration.

Integral equations have been used in biology to formulate

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- the problem of forecasting human population,

- the study of population dynamics such as surges in the birth rate,

- the propagation of stocked fish in a new lake,

to name but a few (Jerri 1999). Many integral equations, such as the equations to formulate the problems mentioned above can be classified into two main categories which are called Fredholm integral equations or Volterra integral equations. Fredholm and Volterra integral equations can be further classified as equations of the "first kind" or the "second kind". An equation is determined to be of the "first kind" if the unknown function appears only under the integral sign, however if the unknown function appears both inside and outside the integral sign an equation is said to be of the second kind. An example of each type of equation will be given below. Take $u(t)$ to be an unknown function to be solved for, $f(x)$ is a given, known function and $K(x, t)$ is a known integral kernel. Then a Fredholm integral equation of the first kind can be expressed as:

$$f(x) = \int_a^b K(x, t) u(t) \, \mathrm{d}t,$$

where a and b are the fixed limits of integration. A Fredholm integral equation of the second kind can then be given as:

$$u(x) = f(x) + \int_a^b K(x, t) u(t) \, \mathrm{d}t.$$

A Volterra equation of the first kind, identified by its variable limit of integration is an integral equation of the form:

$$f(x) = \int_a^x K(x,t)u(t)\,\mathrm{d}t,$$

and a Volterra equation of the second kind is expressed by:

$$u(x) = f(x) + \int_a^x K(x,t)u(t)\,\mathrm{d}t.$$

The importance of an integral equation stems from representing hereditary situations. An integral equation relates the present state of $u(t)$ to the accumulation of changes in its previous values from time, $t = 0$ to present time $t = t$ (Jerri 1985).

The back calculation model from AIDS epidemiology is an integral equation of the first kind and is expressed as:

$$a(t) = \int_0^t h(t - u)f(u)du. \tag{1.1}$$

where $a(t)$ is the new AIDS diagnosis, $f(t)$ is the known incubation period distribution and $h(t)$ is the unknown incidence of HIV infections for which AIDS will eventually be diagnosed (Isham 1989). Equation (1.1) has a variable limit of integration and the unknown function only appears under the integral sign therefore the back calculation model is a Volterra integral equation of the first kind. In chapter 2 and 4 the back calculation model in AIDS epidemiology will be described in detail, its potential as a model to estimate the incidence of opiate use will be discussed, analytical solutions will be produced and estimates of the hidden incidence of opiate use will be obtained.

1.5   Historical Background to Drug Use

For thousands of years, the human race has been using drugs, from cannabis to opiates to the illegal use of prescribed drugs. The human race has used drugs for a variety of reasons, from the need to alter mood, to medicinal remedies for pain relief, to their use for pleasure (O'Kelly 2000). Marijuana, for example, historically has been a legal drug for far longer than it was considered an illegal drug. Marijuana usage for medicinal purposes can be dated back as far as 2737 B.C. in China and from there spread to Europe at least as early as 500 A.D. It wasn't until the late 1900's that marijuana's addictive potential was considered to outweigh any possible medical benefits. The production of opium for pleasure and medical purposes is believed to have first occurred in Eastern Europe and from there spread to the rest of Europe (O'Kelly 2000). Opium was mainly consumed in Europe up to and including the 19th century in the well known form of Laudanum (Booth 1996), which was a mixture of opium dissolved in alcohol in the form of red wine mixed with herbs. Opium was prescribed by physicians in the 19th and early 20th centuries because of its powerfulness. The ready availability of opium as a form of treatment also encouraged physicians to prescribe the drug for medicinal purposes, O'Kelly (2000) noted opium could be bought through pharmacies, by mail order and through both general and drug stores. Morphine, an extremely potent analgesic was first produced by the German pharmacist Serturner in 1803, although the drug heroin wasn't created until 1893 in St Mary's Hospital, Paddington, London. The first large-scale production of heroin was by the German pharmaceutical company Bayer (O'Kelly 2000) and they originally marketed heroin as a cure for morphinism, morphine addiction. According

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to O'Kelly (2000) world governments attempted to control opiate use during the 19th century as a result of the following factors:

- An emerging growth in professionalism in the pharmaceutical and medical disciplines.

- An awareness of the problem of morphine addiction.

- Recognition among socially concerned groups of the implications of the availability and use of different forms of opiates.

1.5.1 Background to Illegal Drug Use in Ireland

Prior to 1969, there was a complete lack of data regarding problem drug use in Ireland. In 1969 a study was conducted on behalf of the Medico-Social Research Board, the aim of the study was to investigate problem drug use among young people in Dublin (Masterson 1970). Dean *et al.* (1985) found that drug use occurred across all social classes and noted that ignorance of the dangers concerning drug use was a common factor in users across all social classes.

Initially there was no particular drug which was commonly used, as there was no market which offered a constant supply of one particular drug, however there was sufficient supply of other drugs to satisfy users. Amphetamines could be purchased over the counter in the 1960's, making them easy to obtain and by 1966 amphetamine dependence was already recognised. Cannabis and Lysergic Acid Diethylamide (L.S.D.) were the most commonly misused drugs in Ireland by the end of the 1960's. However during the 1970's there was a reduction in Lysergic Acid Diethylamide popularity and amphetamine use, this may be attributed to the fact that amphetamines were no longer legally available. Corrigan (1994) noted that de-

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spite the reduction in use of these drugs there was a number of doses of both drugs seized by the Gardaí (the Irish police force) due to availability on the black market.

There have been significant changes in the patterns of cocaine use and availability in Ireland from the 1980's to the present day. In the eighties, cocaine was an extremely expensive drug and tended to be used by higher social economic sections of society (Corrigan 1994). Despite the significant reduction in the production of cocaine, it has become more readily available and less expensive in Europe due to increased production in Columbia. The price of cocaine has reduced drastically in Ireland, from €102 per gram (Moran *et al.* 2001) to €60 to €80 per gram in 2009 (Bracken 2009). Whilst opiates tend to be the most popular drug of misuse there seems to be an association between cocaine use and opiate use, in that opiate users tend to use cocaine as an additional drug (Bellerose *et al.* 2009, National Advisory Committee on Drugs 2007). This connection may be explained by the fact that cocaine reduces the severity of opiate withdrawal (O'Connor 1991).

During the five year period from 1998 to 2002, 2,668 of the individuals presenting of treatment used opiates as their main problem drug whilst using additional drugs (Long *et al.* 2005). Over one fifth of those individuals were also using cocaine, compared to only 167 individuals with a problem of polydrug use, using cocaine as their main problem drug. During the same time period, treatment demand for cocaine use also increased dramatically. Seventy-eight individuals reported cocaine as their main problem drug to the National Drug Treatment Reporting System in 1998; this number had more than trebled by 2002 when cocaine was reported as the main problem drug for 242 treatment cases. This pattern of escalated treatment demand for cocaine use in Ireland from 1998 to 2002 is illustrated in Figure 1.2

below.
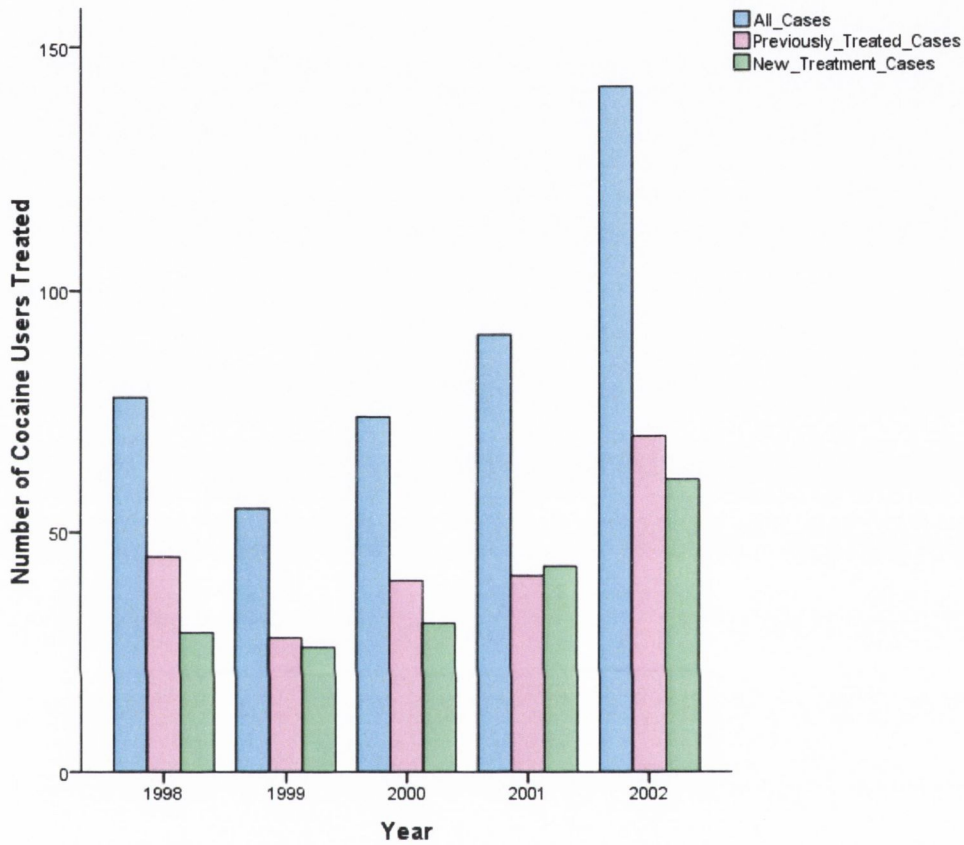
Figure 1.2: Cocaine as the main problem drug of misuse by treatment status, 1998 to 2002 (Long *et al.* 2005).

In more recent times the 2002/2003 National Advisory Committee on Drugs (NACD) general population survey indicated that almost 5% of young adults, aged fifteen to thirty-four had tried cocaine at least once. The substantial and increasing quantities of cocaine seized by the Gardaí is yet another example of the growing cocaine use. Six kilograms of cocaine seized in 1993 was considered to be significant (Gordon 1995) yet in more recent times Gardaí have seized quantities upwards of twenty kilograms.

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In spite of these substantial cocaine seizures it is believed that approximately 540 out of a possible 1,000 tons of cocaine make it onto the black market each year (Corrigan 1994). The steady increase in positive post mortem results and road safety tests in recent years are also indicative of the growing trend in cocaine use (National Advisory Committee on Drugs 2007). The findings of increasing cocaine use in Ireland indicate consistency with the upward trend in cocaine use in Europe National Advisory Committee on Drugs (2007).

Despite the fact that originally there was no particular drug that was commonly used, opiates are the drugs for which most clients seek treatment for in Ireland, this is illustrated in Table 1.1 and Figure 1.3 below.

Year	1990	1991	1992	1993	1994	1995
Drug	%	%	%	%	%	%
Heroin	39.3	37.0	37.9	48.3	55.7	70.6
Morphine Sulphate Tablet	33.0	30.6	26.8	22.5	18.5	10.6
Methadone	1.4	3.0	3.9	5.0	4.4	3.8
Cocaine	0.8	0.4	0.4	0.7	0.3	0.3
Ecstasy	0.0	0.3	2.0	3.5	2.5	3.0
Benzodiazepines	3.0	3.1	2.0	1.2	0.7	1.8
LSD	0.4	0.6	1.3	1.7	1.4	0.8
Volatile Inhalants	2.4	2.2	2.3	1.1	0.7	0.4
Cannabis	11.5	12.6	14.1	10.4	10.1	6.6
Other Drugs	8.0	10.3	9.1	5.6	5.6	2.2
Valid N	2021	2337	2546	2896	2970	3587
Total N	2036	2359	2555	2919	2978	3593

Table 1.1: All treatment contacts in Dublin, by primary drug, 1990 to 1995 O'Brien & Moran (1998).
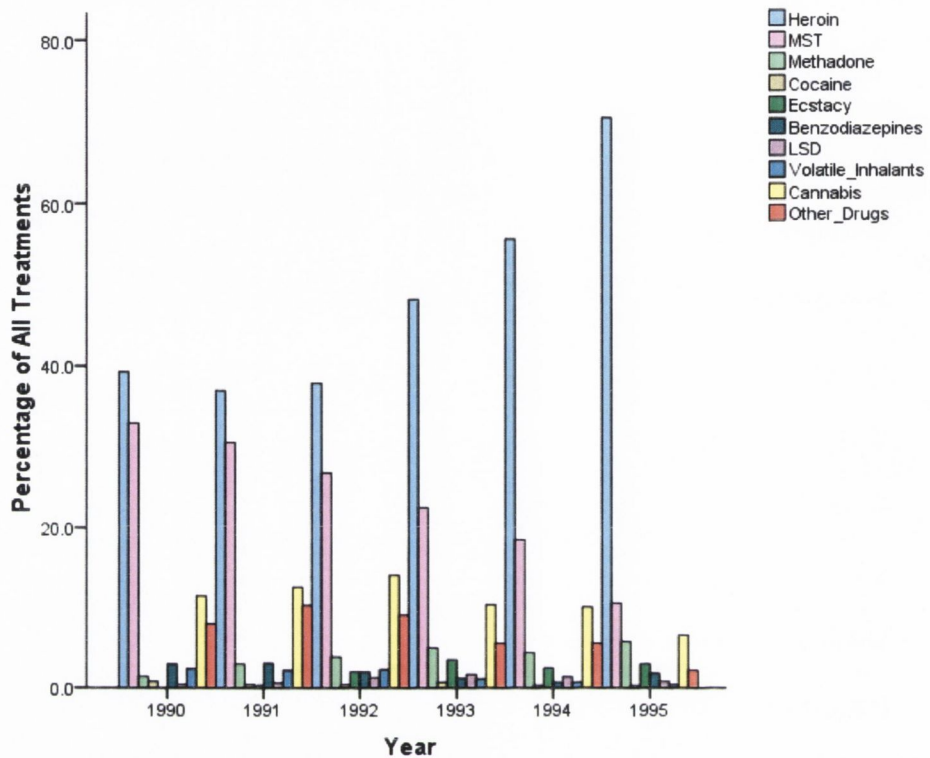
Figure 1.3: All treatment contacts in Dublin, by primary drug, 1990 to 1995 (O'Brien & Moran 1998).

It is evident that drug use continues to be a problem, with drug users substituting one drug for another when difficulty arises in obtaining their drug of choice, as there was a sufficient supply of other drugs to satisfy users needs (Masterson 1970). However literature points to the fact that opiates continue to be the main problem drugs globally (United Nations Office on Drugs and Crime 2007), so it is with this in mind that the history of problem opiate use in the Irish context is examined in the following section.

1.5.2 Background to Problem Opiate Use in Ireland

Opiate use in Ireland dates back at least as far as 1844, when Dr Francis Rynd (1845, p. 167) first described a method of instilling "A solution of fifteen grains of acetate of morphine by using an instrument made for the purpose." Following on from this the hypodermic syringe was developed in Edinburgh in the 1840s. The details of the preparation of the morphia from Turkish opium were first published in the Dublin Pharmacopeia in 1850. The medical community in Ireland was increasingly concerned with the problem of morphine addiction and Dr. H.C. Drury addressed the Royal Academy of Medicine to discuss morphine addiction in 1899. Drury discussed the problems linked to free use of morphine and noted that these problems were particularly prevalent among the medical profession.

The heroin epidemic in Ireland occurred much later than the epidemic occurred in its European counterparts (O'Brien & Moran 1998). The explanation for this is Ireland's western position on the continent; therefore it took longer for the opiates to arrive here. At the beginning of the eighties there was an abrupt increase in opiate use among the young people of inner city Dublin (O'Brien & Moran 1998). It is believed that the opiate epidemic in Dublin commenced in the early eighties and peaked in 1983. Considerable quantities of heroin became available to the world market as a result of the Iranian revolution and hence the commencement of heroin misuse. In 1979 there were 294 patients attending the National Treatment Centre at Jervis Street hospital of which 182 were opiate users. The average number of patients attending Jervis Street hospital for heroin addiction increased from five per month in 1979 to 239 per month in 1983, this dramatic increase was further evidence of an escalating opiate problem in Dublin. A scarcity of heroin, as a result

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of increasing heroin seizures between 1980 and 1986 led to the misuse of synthetic opiates such as buprenorphine and morphine (Gordon 1995).

The percentage of first treatments and all treatments that used opiates as their primary drug fluctuated between 1990 and 1995, yet there was an overall pattern of increasing treatment demand for opiate use. The lowest proportion of individuals seeking treatment for opiate use was made in 1993, with approximately 75% of all treatment and 49% of first treatment sought by clients with opiates as their primary drug of misuse. The proportion of treatment contacts presenting with opiates as the primary drug of misuse is illustrated in Table 1.2 below.

Year	All Treatments Total (%)	First Treatment Total (%)
1990	2037 (**79.2**)	624 (**60.3**)
1991	2359 (**77.7**)	450 (**49.6**)
1992	2555 (**75.1**)	668 (**48.5**)
1993	2919 (**79.1**)	859 (**64.1**)
1994	2978 (**82.1**)	1150 (**74.3**)
1995	3593 (**86.8**)	1396 (**77.2**)

Table 1.2: Treatment contacts presenting with opiates as their main problem drug of misuse. Source: O'Gorman (1998, p. 160).

Opiate use is a hidden phenomenon due to the fact that it is an illegal activity in Ireland. It was and still is generally excepted by experts in the field that figures for opiate use are grossly underestimated. Although the numbers presenting for

treatment for all drug use, including opiate use is recorded, the first estimates of the prevalence of opiate use in Dublin were produced by Comiskey & Barry (2001). Comiskey & Barry (2001) estimated there were 13,460 opiate users in Dublin which was over three times more than the figure of 3,840 recorded by the National Drug Treatment Reporting System as using opiates as their main drug of misuse. From 1998 to 2002 the number of new cases attending for treatment stating opiates as the main drug of misuse declined however in the same time period the number of all cases presenting for treatment with opiates as the primary drug of misuse rose from 4,479 to 5,742 (Long *et al.* 2005). Kelly *et al.* (2003) produced the first national prevalence figures for opiate use for Ireland for 2000 and 2001. Kelly *et al.* (2003) suggests figures of 14,158 and 14,452 as the estimated prevalence of opiate users for the whole of Ireland for 2000 and 2001 respectively. These figures were further broken down to suggest point estimates of 12,268 and 12,456 for Dublin for 2000 and 2001 respectively.

Opiate use was originally confined to the Dublin area with pockets of use around the country (Merchants Quay Ireland 2006), however in more recent times there has been a growing trend in opiate use outside of the Dublin area. The Health Research Board findings that Carlow, Waterford, Louth and Wexford had the highest average incidence of treated drug use for the period between 2001 and 2006 (Alcohol and Drug Research Unit of the Health Research Board 2009) and the establishment of drug treatment facilities throughout Ireland are further evidence that drug use is no longer limited to the Dublin area. A study was conducted on problem drug use in the Midland Regional Drugs Task Force (MRDTF) region and heroin was found to be the most common problem drug used for those in treatment, with approximately

100% increase in opiate use in Offaly and Longford between 2004 and 2007 (Lyons *et al* 2010). The report also found that there were excessively long waiting lists for opiate users accessing treatment such as the methadone maintenance program and a total lack of residential abstinence and rehabilitation facilities in the Midland Regional Drugs Task Force region.

It is evident that the problem of illicit drug use in Ireland has escalated in the last forty years and what was once a problem mainly in the Dublin area has now spread nationwide. However it is imperative to note that illicit drug use is recognised as a problem and the following sections document the history of drug treatment policy and legal policies implemented in a bid to tackle this problem in Ireland.

1.5.3 History of Irish Drug Policy
Treatment Policy

For the purpose of this work we use the National Drug Treatment Reporting System's definition of treatment. Treatment is defined as any activity which aims to improve the psychological, medical or social state of individuals who seek help for their drug problem (Alcohol and Drug Research Unit of the Health Research Board 2007). Medication free therapies and medically assisted treatment are the two principles on which treatment services are built. Medically assisted treatment options include detoxification, methadone reduction and substitution programmes while counselling, group therapy and psychotherapy are examples of medication free therapies (Alcohol and Drug Research Unit of the Health Research Board 2007).

Treatment services can be further classified, with some services providing an abstinence based approach and others concentrating on a harm reduction approach. The abstinence approach caters for drug free clients focusing on maintaining a drug

free lifestyle by providing psychological support and a structured schedule of daily activities which clients must attend (Comiskey *et al.* 2009). Abstinence based treatment is available in an inpatient setting known as residential rehabilitation and an outpatient setting known as structured day programmes. Up to the late 1980's drug policy was dominated by abstinence approaches which were adopted by the Coolmine Therapeutic Community and Trinity Court (Cullen 1994). However as a result of the growing HIV problem in the mid 1980's in Ireland the needle exchange programme, a harm reduction service, was established.

In 1989 five needle exchanges were set up to provide sterile injecting equipment and materials such as sterile water and swabs (Alcohol and Drug Research Unit of the Health Research Board 2008b). According to Cox & Robinson (2008) the three main objectives of the needle exchange programme where;

- To reduce the prevalence of blood borne viruses.

- To educate drug users of the risks associated with injecting drug use and unsafe sexual practices.

- To engage with injecting drug users and refer them on to treatment services.

In 2008 there were thirty four needle exchanges operating in Ireland consisting of fixed-site exchanges, home visit exchanges and exchanges in public locations. According to Cox & Robinson (2008) needle exchanges have contributed to low or reduced spread of HIV among injecting drug users, reduced levels of needle sharing and individuals in maintaining low levels of risk.

Another form of drug treatment is structured detoxification which involves individuals being safely withdrawn from opiates under medical supervision. Structured

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detoxification is available in both in-patient and out-patient facilities. Methadone is the most commonly used agent for opioid detoxification in Ireland. This form of detoxification, known as methadone reduction, is where an individual is given gradually reducing doses of methadone usually over a four to twelve week period until the individual is opiate-free.

Substitution treatment is a medically supervised form of drug treatment used in Ireland. This treatment is provided by treatment centres, satellite clinics and GP's. Methadone, introduced in 1992, buprenorphine, introduced in 2002 and the buprenorphine/naloxene, combination introduced in 2007 are all agents used for opiate substitution treatment. Methadone maintenance was established as a harm reduction service and is the most commonly used agent for heroin and other opiate substitution treatment. The Central Treatment List (CTL) was established in 1993 to regulate and control the dispensing of methadone (Department of Health and Children 2005). The Central Treatment List is a register of all clients receiving methadone as treatment for problem opiate use in Ireland and insures that clients can obtain there methadone from one source only.

Legal Policy

Although world governments initially recognised that illegal opiate use was a problem in the nineteenth century and procedures were implemented to control illegal opiate use, Irish drug policy did not originate until the 1960's. Prior to the 1970's the general consensus was that Ireland had managed to avoid a serious drug problem, it was however accepted that unless a constant effort was maintained to prevent the abuse of habit forming drugs, a serious drug problem would be inevitable (Masterson 1970). On recognition of the fact that without intervention a serious drug problem

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would be imminent, policies and procedures, which would go on to be developed and improved, were implemented in an effort to control problem drug use.

In the latter half of the 1960's there was a dramatic increase in the numbers appearing before the courts on drug related charges, from only one individual appearing in 1965 to fifty four individuals appearing before the courts by October 1969 (Masterson 1970). Although a serious drug problem had not yet developed, the Garda drug squad was established in 1968 in response to a growing awareness of drug misuse among the public. A year later the first statutory outpatient drug treatment facility, the National Advisory and Treatment Centre was founded at Jervis Street Hospital in Dublin. Despite growing public awareness of problem drug use, progress with regard to legislation was slow, as the Misuse of Drugs Act, which provided a wide variety of controls over drugs susceptible to misuse was not passed until 1977.

In a bid to tackle the increasing problem of drug use, existing legislation was updated, new legislation was passed and new task forces were established. The Road Traffic Act was amended in 1978 to include driving under the influence of an intoxicant, which is defined as drugs or alcohol, which renders the ability to control the vehicle as an offence. A special Government Task Force was launched in the Department of Health in 1983. Although the task force report was not published it resulted in the enactment of The Misuse of Drugs Act (1984), which prevented the printing or sale of magazines or books which promoted the use of drugs or advertised drug equipment. A new National Coordinate Committee on Drug Abuse was setup in 1985 on the recommendation of the Government Task Force (O'Brien & Moran 1998). The Criminal Justice (Drug Trafficking) Act, 1996 was passed which allowed

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for individuals accused of drug trafficking charges to be detained for up to seven days and also allow the courts to draw inferences from the failure of the accused to mention particular facts during questioning. The Criminal Assets Bureau was launched in 1996 was to identify and confiscate criminally obtained assets. These assets are confiscated through the application of the Proceeds of Crime Act, 1996 which allows for freezing and removal of the proceeds of crime (Moran *et al.* 2001).

The amendments to existing policies and the establishment of new task forces discussed, demonstrate policy makers commitment to controlling the illegal use of drugs. Irrespective of this, drug use continues to be a problem and some modelling has been done on problem drug use which will be discussed further in the next section.

1.6 Mathematical Modelling and Illegal Drug Use

In spite of the body of research on the mathematical modelling of epidemics little has been done to apply the models to the worldwide problem of increasing and expanding substance misuse. Bobashev *et al.* (2007) discuss the difficulties involved in applying mathematical models in drug use research, namely the availability of reliable data and the absence of clear, long term markers of drug use.

Hunt & Chambers (1976) were among the first researchers to attempt applying models to the drug use epidemic in the United States. Leon Hunt and Carl Chamber's book the "Heroin Epidemic', in which they developed a theory for the spread of drug use in a bid to estimate trends in incidence of drug use was published in 1976. Hunt & Chambers (1976) pioneering work focused on the micro-diffusion and macro-diffusion processes.

Micro-diffusion, how drug use spreads from individual to individual, depends on a drug users tendency to spread drug use to new users similar to the transmission of communicable diseases. Macro-diffusion, how drug use spreads from region to region, describes the geographical spread of drug use across boundaries. However as a result of criticism of the proposed methods at the time there was no development to the models (Hickman 2006). Although the assumptions and methods proposed by Hunt and Chambers were proven not to be correct by Hickman *et al.* (2001), Hickman (2006) acknowledges that they were a useful starting point and questions the difference in progress to date had Hunt and Chambers insights been taken on board at the time.

It was then proposed that methods from AIDS epidemiology be adapted and applied to drug use epidemiology (Comiskey & Hay 2001). Initially epidemiological models of HIV transmission included drug use as a critical component, yet models with the sole purpose of describing or understanding the drug use epidemic were lacking (Bobashev *et al.* 2007). With the exception of models by Behrens *et al.* (1999), Reuter (2001) and Rossi (2002) this resulted in very few publications of models. A continuous time model was proposed by Behrens *et al.* (1999) in an effort to gain insight into how drug use epidemics should be studied and controlled. They applied a dynamic model of drug demand and initiation processes to new use using differential equations. It was concluded from the model that the effectiveness of drug control interventions such as treatment, depends on the stage of the epidemic at which it takes place. Rossi (2002) presented a compartmental model for reproducing an epidemic of problematic drug use. The model presented is a combination of an SIS and an SIR model. The SIS compartmental model has two classes, the susceptible

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class and the infected class. It can be used to model a situation where susceptible individuals become infected, these individuals then recover and become susceptible again. An SIR compartmental model has three classes, the susceptible class, the infected class and the recovered classed. The SIR model can be used to represent a situation where the susceptible individuals become infected, recover and become immune. The conclusions drawn from the model analysis are that the spread of infectious disease epidemic is related to the hidden part of the drug users career and therefore the objective of intervention should be to reduce the length of the latency period of the drug using career, where the latency period is the hidden part of the drug-using career.

The EMCDDA (2001) suggest that modelling based on mathematical theory is a useful tool to estimate the prevalence and incidence of opiate use or to aid understanding of drug processes. The EMCDDA (2001) reiterate the fact that little has been done to apply mathematical models to drug-use epidemiology. It published the monograph "Modelling Drug Use: Methods to Quantify and Understand Hidden Processes" which suggests models to estimate prevalence and incidence of opiate use such as the back calculation model, compartmental models, which were discussed briefly in previous sections, multiple indicator methods, dynamic models and structural equations. The multiple indicator method is a prevalence estimation technique which can be applied to the problem of estimating the size of the opiate epidemic. This technique is discussed in detail along with the capture-recapture method, the multi-source enumeration method and the multiplier method in chapter 5.

Using the techniques described in the EMCDDA Monograph, national prevalence studies have been conducted to estimate the scale of problem opiate use in Ireland.

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In more recent times, White & Comiskey (2007) identified a gap in knowledge with regard to the drug using career which they explain consists of initiation, habitual use, treatment relapse cycle and recovery. The authors proposed a compartmental model for the opiate using career and its parameters which is expressed by:

$$\frac{dS}{dt} = -\gamma - \frac{\beta_1 U_1 S}{N},$$

$$\frac{dU_1}{dt} = \frac{\beta_1 U_1 S}{N} - pU_1 + \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_1)U_1,$$

$$\frac{dU_2}{dt} =, pU_1 - \frac{\beta_3 U_1 U_2}{N} - (\mu + \delta_2)U_2$$

$$(1.2)$$

where the parameters of the model are:

- S: the number of susceptible individuals in the population.

- γ: the number of individuals from the general population entering the susceptible population.

- β_1: the probability of becoming a drug user.

- U_1: the number of drug users not in treatment.

- N: the size of the total population.

- p: the proportion of drug users entering treatment.

- β_3: the probability of a drug user in treatment relapsing.

- U_2: the number of drug users in treatment.

- μ: the natural death rate of the population.

- δ_1: a removal rate which includes drug related death of a drug user not in treatment and recovery.

- δ_2: a removal rate which includes the drug related death of a drug user in treatment and successful recovery.

The conclusion drawn from the model analysis is that prevention is better than cure, therefore it is more effective to prevent drug use than to control drug use by increasing the numbers accessing treatment. Work on modelling drug use both nationally and internationally is limited. The literature suggests however that models for the purpose of estimating the true size of the epidemic, the geographical spread and to provide a general understanding of the epidemic are essential.

The objective of this thesis as discussed in section (1.1) is to estimate prevalence, incidence and geographic spread of opiate use and therefore the key elements of the models produced will be the number of first treatment contacts and the rate of progression to first treatment for opiate use. However, it is worth mentioning that there are many other elements which could be included when developing mathematical models for opiate use depending on the purpose of the model. Sussman & Ames (2008) found that individuals are differentially vulnerable to opiate use however there are certain factors that are known to increase the risk of initiation to opiate use. Genetic, familial and sociological bases are just some of the factors which make individuals more susceptible to opiate use. Swan (1995) and Merikangas *et al.* (1998) found that a family history of drug use was a predictive factor which influ-

enced an individuals initiation into drug use. It is widely believed that drug use is passed from generation to generation, an individual has a predisposition to abusing a particular drug, for example opiates, if their parents have struggled with addiction to the same drug (Swan 1995). Another risk factor which increases vulnerability to opiate use is mixing patterns, non-drug users can be coerced into drug use by influential peers. A factor which is particularly relevant in the current economic climate is social deprivation, Greaves (2003) found people in areas with high levels of social and economic deprivation and marginilisation are also more susceptible to drug use. Initiation to opiate use can be influenced by all of these factors, nevertheless, it is not practical to produce a mathematical model which accounts for all of them.

Mathematical models which contain too many different elements can be complex and are often difficult, sometimes even impossible to solve. Therefore it is more beneficial to keep models simple, as mentioned in section (1.2) on the modelling process and only include the most relevant factors for the estimates required. The models for prevalence, incidence and geographic spread of opiate use will not have direct elements to account or the effect of social deprivation, however, the numbers and times to first treatment will be modelled allowing for changes as a result of cuts in funding, increased treatment demand and waiting times for treatment services.

1.7 Discussion and Conclusions

Problem opiate use is recognised in Ireland and as a result, the numbers entering treatment for opiate use are well documented by the Health Research Board. A vast array of studies have been conducted, at great expense in order to produce estimates of the size of the opiate epidemic, nevertheless precise estimates are extremely dif-

ficult if not impossible to obtain. The fact that opiates are the primary drugs of misuse for treatment contacts at national and international level is well documented (United Nations Office on Drugs and Crime 2007), as is the number of treatment contacts for opiate use, yet there is still an identified gap in researchers' and policy makers' knowledge with regard to the numbers being initiated to drugs (Behrens *et al.* 1999). As a result, the scope of decision-making for measures of prevention and intervention is severely limited. This thesis endeavours to produce models which will enable policy makers and service providers to anticipate the number of potential future treatment contacts for opiate use in a bid to tackle the very real problem of ongoing drug use and provide adequate treatment services.

1.8 Chapter Summary

This chapter introduced the subject of the thesis, to derive models for the prevalence, incidence and geographic spread of opiate use and outlined how the models will be derived and developed from chapter to chapter. The modelling process was then introduced and an introduction to the history of mathematical modelling in epidemiology was depicted. Integral equations were proposed as a starting point for this research and were therefore discussed in some detail. It went on to discuss problem drug use, the scale of the drug problem in Ireland and how Irish drug policy has evolved in line with changes in the pattern of drug use. Finally the chapter discussed mathematical modelling in epidemiology.

Chapter 2

Estimating the Incidence of Hidden, Untreated Opiate Use

2.1 Introduction

In a global climate of significant problem drug use, ongoing and widespread heroin use, the increase in cocaine use across all aspects of society and the increasing and illegal use of controlled drugs, the EMCDDA (2001) believe that one of the first questions to be addressed is to identify the scale of the problem. Illegal drug use is, by its nature, a hidden phenomenon and estimates of the true size of the epidemic are difficult to obtain, however policy makers and service providers are particularly interested in this estimate. For the purpose of this research, *incidence* is defined as the number of new cases of untreated opiate use in a defined population within a specified time period and *prevalence* is defined as the total number of cases of opiate use in a given population at a designated time (Last 2001). With the exception of work by De Angelis *et al.* (2004) in England and Ravà *et al.* (2001) in Italy, estimates of the incidence of illegal drug use are very rare, yet viable cost effective methods to produce incidence estimates are vital for the planning and provision of effective drug treatment services.

Estimates of the hidden incidence of drug use enables policy makers and service

providers to allocate increasingly scarce resources accordingly, as these estimates provide insight in the number of potential first treatment clients in the future. Illegal drug use is recognised as a problem worldwide, however according to United Nations Office on Drugs and Crime (2004) opiates continue to be the main problem drugs of misuse at a global level, with this in mind, the specific aims of this chapter are:

- To derive a viable method to produce current and regular estimates of the incidence of untreated opiate use.

- To use the technique developed to estimate for the first time the incidence of untreated opiate use in Ireland from 1999 to 2005.

2.2 Methodology

Previous use of the back calculation model to predict the incidence of disease, particularly AIDS, in the United States, U.K. and Ireland is well documented (Brookmeyer & Gail 1988, Brookmeyer & Damiano 1989, Isham 1989, Comiskey & Ruskin 1992). Within the HIV and AIDS epidemiology the back calculation method works on the premise that one can back calculate from the known reported AIDS cases, through the use of the known incubation period distribution, to provide an estimate of the unknown and undiagnosed HIV cases. Hence with back calculation two of the three components of the equation (2.1) below, $T(t)$, $U(t)$ and $f(t)$ must be known. Using the knowledge of the two known components, it is then possible to derive the third unknown component of the model from equation (2.1). Isham (1989) noted that the back calculation method relies on the assumption of the incubation period distribution and is dependent on accurate AIDS incidence data therefore careful consideration must be given when choosing models for the two known components.

The back calculation method has been constantly adapted to allow for changes in the components of the model and to account for reporting delays (Brookmeyer & Gail 1988, Brookmeyer & Damiano 1989, Isham 1989, Comiskey & Ruskin 1992, Comiskey 2001) these enable researchers to produce better incidence estimates.

The back calculation model may be expressed in the form,

$$T(t) = \int_0^t U(t-u)f(u)\,du, \tag{2.1}$$

where, in the substance use or opiate use application, $T(t)$ is the known rate of new first treatment contacts for opiate use, $U(t)$ is the rate of hidden, untreated opiate use, which is defined as opiate users who have never received any form of treatment for opiate use in the past and $f(t)$ is the rate of progression to first treatment for opiate use. Using equation (2.1) the number of hidden opiate users can be estimated for a given year. By taking the known number of first treatment contacts for opiate use combined with published estimates of the average time to treatment it is possible to calculate the number of opiate users who have never been treated before, at a specified time.

(Comiskey & Hay 2001), were one of the first to propose the method of back calculation in this regard, suggesting that the approach used in estimating the hidden HIV incidence, could be applied to the problem of estimating the hidden untreated incidence of drug use from cases of known drug use.

The Empirical Bayesian back calculation approach was suggested as a method to estimate the incidence of injecting drug use from data observed on drug users seeking treatment in Italy (Rossi 1999). However the lack of available data on the latency period distribution, that is the time from first heroin use to first treatment,

meant that it was impossible to demonstrate the application of the method to real national or international data. The method was explored to estimate long-term trends in injecting drug use in England, De Angelis *et al.* (2004) concluded that while the method was worthwhile, better information on overdose mortality and cessation rates would improve the method and make it more realistic.

Within this chapter the back calculation model (2.1) is adapted and analytically solved to obtain solution for the incidence of untreated drug use. In particular the model is applied specifically to the problem of opiate use. An opiate user is defined to be someone who has used an opiate such as heroin, illegal methadone or other opiates such as dihydrocodeine (DF118) or buprenorphine. The original analytical approach to the solution of the integral equation is presented and the method is illustrated with the first application to Irish data.

2.2.1 The Number of New Cases of Treated Drug Use, T(t)

Three models are chosen to describe the number of new treatment contacts for opiate use, $T(t)$, of equation (2.1). The first form chosen is,

$$T(t) = a_0 \exp(a_1 t), \tag{2.2}$$

where a_0 and a_1 are constants and t is the time variable. Equation (2.2), describes a rapid change positive or negative initially in the numbers presenting for first treatment for opiate use, with the numbers presenting for first treatment changing slowly as t increases. This rapid change may be in response to a positive urgent intervention for example where the number of new treatment places increases. This change could also be explained by the suspension of funding available for treatment facilities

as result of the current worldwide recession.

The second form chosen to model $T(t)$ is,

$$T(t) = b_0 + b_1 t, \qquad (2.3)$$

where b_0 and b_1 are constants and t is the time variable. Equation (2.3), describes a linear relationship in the numbers presenting for first treatment for opiate use. This model may be appropriate in a setting where new treatment facilities have been introduced or where the number of places in existing treatment facilities are expanding or contracting at a constant rate.

The final form chosen to model $T(t)$ is,

$$T(t) = c_0 + c_1 t^2, \qquad (2.4)$$

where c_0 and c_1 are constants and t is the time variable. The quadratic model for $T(t)$ considered in equation (2.4), describes a slow change initially in the numbers entering first treatment, with the numbers entering treatment changing more rapidly as t increases. This model may be suitable in a situation where there is staggered intervention or suspension of funds over a period of time.

These three forms of $T(t)$ are used to model the incidence of first treatment contacts for opiate use over the range of values for which $U(t)$, the number of opiate users not in treatment, will be estimated.

2.2.2 The Rate of Progression to First Treatment for Opiate Use, f(t)

The Gamma and Weibull distributions describe the probability of the value of a random variable falling within a particular interval. These distributions have been

widely used in the past to model the incubation period distribution of diseases such as AIDS, SARS, smallpox and H1N1pdm (Brookmeyer & Gail 1988, Rao & Kakehashi 2005, Isham 1989, Nishiura 2009, Ghani et al. 2009, Farewell et al. 2005). In more recent times Rossi (1999) applied these models to the problem of modelling the latency period of problem drug use in London, The Netherlands, Italy and Portugal.

The length of times between first opiate use and first treatment contact are assumed to be independent and identically distributed variables with probability density function f. The Gamma and Weibull distributions are considered to be viable distributions to model times to treatment from initial opiate use as these distributions measure time to failure, i.e. the time from commencement of opiate use to the time when an individual fails to be an untreated opiate user (presents for treatment).

The Gamma distribution with parameters α and λ, is denoted by $\Gamma(\alpha, \lambda)$, with probability density function,

$$f(t) = \frac{\lambda(\lambda t)^{\alpha-1} \exp(-\lambda t)}{\Gamma(\alpha)}, \tag{2.5}$$

for $t \geq 0$ and mean, $\mu = \frac{\alpha}{\lambda}$.

The Weibull distribution is denoted by $\omega(\beta, \rho)$, with probability density function,

$$f(t) = \beta\rho(\rho t)^{\beta-1} \exp\{-(\rho t)^\beta\}, \tag{2.6}$$

for $t \geq 0$ and mean, $\mu = \rho^{-1}\Gamma(1 + \frac{1}{\beta})$, where $\Gamma(1 + \frac{1}{\beta})$ is the gamma function which returns a single value.

2.2.3 Analytical Solutions for the Untreated Incidence of Opiate Use, U(t)

New analytical solutions are determined for equation (2.1) given certain assumptions about the parameters of the incubation period distribution, $f(t)$. It is possible to determine analytical solutions for $U(t)$ in equation (2.1) when $T(t)$ is described by equations (2.2), (2.3) and (2.4) and $f(t)$ is modelled by equations (2.5) and (2.6). The first case considered is when $f(t)$ is modelled by the Gamma distribution in equation (2.5), with $\Gamma(\alpha = 1, \lambda)$, to give,

$$T(t) = \int_{u=0}^{t} U(t-u)\lambda \exp(-\lambda u)\, du. \tag{2.7}$$

To solve the integral in equation (2.7) for $U(t)$, a change of variables is made. Letting $s = t - u$, when $u = 0$ then $s = t$, when $u = t$ then $s = 0$ and $-\,ds = du$. This change of variables was substituted into equation (2.7) to give,

$$T(t) = \int_{s=0}^{t} U(s)\lambda \exp(-\lambda(t-s))\, ds. \tag{2.8}$$

Equation (2.8) was differentiated using Leibnitz rule (Thomas *et al.* 2007) for the derivative of an integral to give,

$$\frac{dT}{dt} = \int_{0}^{t} U(s)\lambda\,(-\lambda) \exp(-\lambda(t-s))\, ds + \lambda U(t). \tag{2.9}$$

Equation (2.9) was divided by λ and was rearranged to give,

$$U(t) = \frac{1}{\lambda}\frac{dT}{dt} + T(t), \tag{2.10}$$

an analytical solution for the unknown $U(t)$ in terms of the known $T(t)$.

The second case considered was when the rate of progression to treatment, $f(t)$ was modelled by a Gamma distribution denoted by $\Gamma(\alpha = 2, \lambda)$, then

$$T(t) = \int_0^t U(t - u)\lambda^2 u \exp(-\lambda u)\, du. \qquad (2.11)$$

In order to solve the integral in equation (2.11) for $U(t)$, as before a change of variable was made by letting $s = t - u$, when $u = 0$ then $s = t$ and when $u = t$ then $s = 0$, which gives

$$T(t) = \int_0^t U(s)\lambda^2(t - s)\exp(-\lambda(t - s))\, ds. \qquad (2.12)$$

Leibnitz rule for differentiating under the integral sign was used to give,

$$\frac{dT}{dt} = \int_0^t U(s)\lambda^2 \exp(-\lambda(t - s)) - U(s)\lambda^3(t - s)\exp(-\lambda(t - s))\, ds. \qquad (2.13)$$

Equation (2.13) was differentiated to give,

$$\frac{d^2T}{dt^2} = \int_0^t U(s)\lambda^4(t-s)\exp(-\lambda(t-s)) - 2\lambda^3 U(s)\exp(-\lambda(t-s))\, ds + U(t)\lambda^2. \qquad (2.14)$$

which was divided by λ^2 and rearranged to give,

$$U(t) = \frac{1}{\lambda^2}\frac{d^2T}{dt^2} + \int_0^t -\lambda^2 U(s)(t-s)\exp(-\lambda(t-s)) + 2\lambda U(s)\exp(-\lambda(t-s))\, ds. \qquad (2.15)$$

A solution for $U(t)$ was obtained by taking equations (2.12), (2.13) and (2.15), to give,

$$U(t) = \frac{1}{\lambda^2}\frac{d^2T}{dt^2} - T(t) + \frac{2}{\lambda}\left(\frac{dT}{dt} + \lambda T(t)\right) \qquad (2.16)$$

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The coefficients of $T(t)$ were added to give,

$$U(t) = \frac{1}{\lambda^2}\frac{d^2T}{dt^2} + \frac{2}{\lambda}\frac{dT}{dt} + T(t). \tag{2.17}$$

Using the same approach it can be shown that when the rate of progression to treatment is represented by a Gamma distribution, denoted by $\Gamma(3, \lambda)$, the following solution is produced for $U(t)$,

$$U(t) = \frac{1}{\lambda^3}\frac{d^3T}{dt^3} + \frac{3}{\lambda^2}\frac{d^2T}{dt^2} + \frac{3}{\lambda}\frac{dT}{dt} + T(t). \tag{2.18}$$

It can be seen from equations (2.10), (2.17) and (2.18) that the order of $U(t)$ is given by the value of α when $\alpha \in \mathbb{N}$, and the coefficients of $U(t)$ are binomial in form.

Further analytical solutions for $U(t)$ in equation (2.1) are considered when $f(t)$ is modelled by the Weibull distribution in equation (2.6), with $\omega(\beta = 1, \rho)$. The change of variables, $s = t - u$, when $u = 0$ then $s = t$, when $u = t$ then $s = 0$ and $-ds = du$, is made to give,

$$T(t) = \int_0^t U(s)\rho\exp\{-(\rho(t-s))\}\,\mathrm{d}s. \tag{2.19}$$

Equation 2.19 is differentiated using Leibnitz rule to give,

$$\frac{dT}{dt} = \int_0^t U(s)(-\rho^2)\exp\{-(\rho(t-s))\}\,\mathrm{d}s + \rho U(t). \tag{2.20}$$

Equation (2.20) is divided across by ρ and rearranged to give,

$$U(t) = \frac{1}{\rho}\frac{dT}{dt} + T(t), \tag{2.21}$$

which is of the same form as equation (2.10).

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In the case of the Weibull distribution it is not possible to determine $U(t)$ analytically when $\beta > 1$, as the integral of a quadratic exponential is required. If the Weibull distribution is chosen, equation (2.1) must be solved numerically. In order to do this a change of variables is made again. For $\omega(2, \rho)$, this gives

$$T(t) = \int_0^t U(s) 2\rho(\rho(t-s)) \exp\{-(\rho^2(t-s)^2)\} \, ds, \tag{2.22}$$

which is a linear Volterra equation of the first kind. Equation (2.22) is differentiated twice using Leibnitz rule and divided across by $2\rho^2$ to get,

$$\frac{1}{2\rho^2} \frac{d^2 T}{dt^2} = \int_0^t U(s) \left(4\rho^4(t-s)^3 - 6\rho^2(t-s) \right) \exp\{-(\rho^2(t-s)^2)\} \, ds + U(t). \tag{2.23}$$

Equation (2.23) is of the form of a Volterra equation of the second kind, which can be solved numerically for $U(t)$ using the C++ program LU decomposition.

2.3 Results

Analysis of treated drug use, particularly opiate use, including heroin and other illegal opiates is based on data supplied by the Health Research Board. In equations (2.2), (2.3) and (2.4) for $T(t)$ and $f(t)$, $t = 1$ corresponds to 1999, the first year for which data was available for analysis. $T(t)$ is based on the National Drug Treatment Reporting System data on the number of first treatment contacts for the seven year period from 1999 to 2005.

2.3.1 Results - New Cases of Treated Opiate Use, T(t)

The observed first treatment numbers provided by the Health Research Board for 1999 to 2005 can be seen in Figure 2.1.
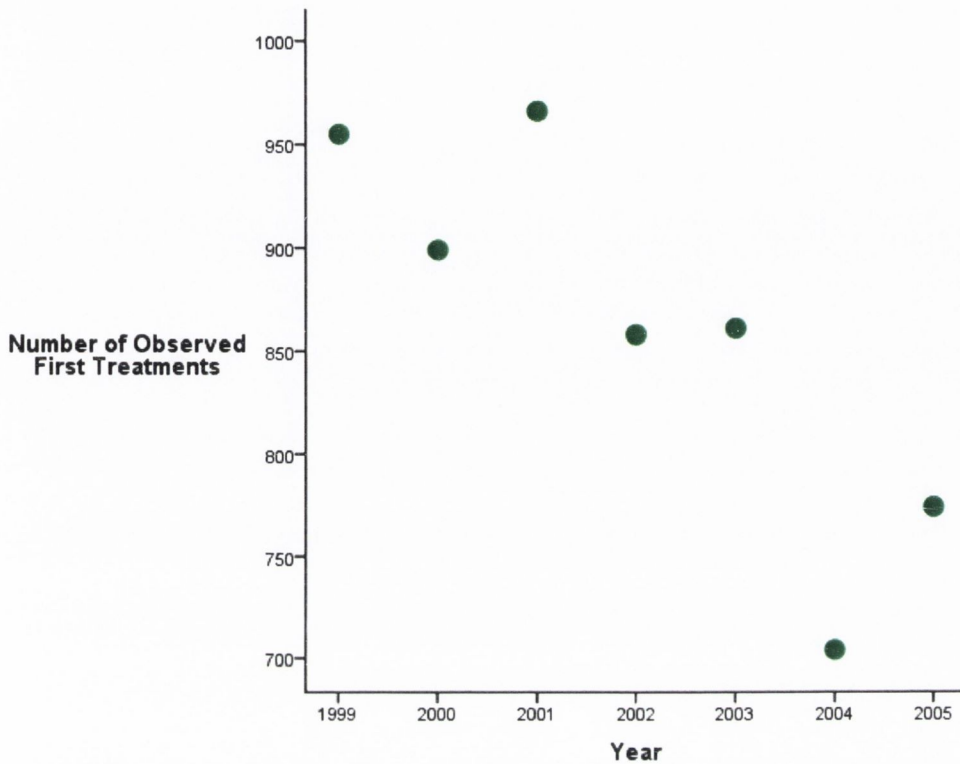
Figure 2.1: Observed number of first treatments of opiate use from 1999 to 2005. Source: private communication, Dr Jean Long, Health Research Board, Spring 2009.

Simple regression is used to describe the rate of new opiate treatment contacts by fitting equations (2.2), (2.3), and (2.4) to the observed data in Table 2.2 below, which is discussed in detail in chapter 3. In order to describe the data a regression equation is fitted to the observed data, where year is the independent variable t and the number of first treatments is the dependent variable y.

The simple linear regression equation which is also known as the least squares regression equation is one of the models considered. The best fitting regression line is selected using the least squares method based on the fact that the sum of squared residuals, which are the differences between the observed values and the values pre-

dicted by the regression equation squared, are as small as possible. The exponential

model is also considered to model the curved relationship in the data on first treat-

ment contacts and time t. An exponential function of the form $y = a\exp(bt)$ is fitted

to the data by performing a least squares fit using the transformed model function

$ln(y) = a + bt$. The pth-order polynomial regression model can be used to model

situations were y changes in relation to t displaying one or more curves (Bowerman

& O'Connell 2000). Bowerman & O'Connell (2000) states that occasionally third or

higher order polynomial models are useful although a 2nd order polynomial model

is appropriate to model most curved regression relationships. Therefore a 2nd or-

der polynomial model, known as a quadratic regression model is also fitted to the

observed data.

The resulting estimates of the model coefficients the R^2 and the $\bar{R}^2$ values are

presented in Table 2.1 below.

Model	Parameter Estimates	(Std. Error)	R^2	$\bar{R}^2$
Exponential	$a_0 = 1015.52$ **(52.082)**	$a_1 = -0.043$ **(0.012)**	0.71	0.65
Linear	$b_0 = 1007.86$ **(46.35)**	$b_1 = -37.07$ **(10.36)**	0.72	0.66
Quadratic	$c_0 = 950.96$ **(31.97)**	$c_1 = -4.57$ **(1.24)**	0.73	0.68

Table 2.1: Parameter estimates of $T(t)$ with standard errors (Std. Error).

From the R^2 values it can be observed that each of the models chosen fit the data

well, with over 70% of the variation in the observations explained by the regression

models. The $\bar{R}^2$ value is included as it corrects for the increase in R^2 as a result of

adding an unimportant independent variable to the model (Bowerman & O'Connell

2000). $T(t)$ describes the rate of new treatment contacts for opiate use, therefore in order to obtain the expected number of first treatment contacts in any particular time period, $T(t)$ must be integrated, thus,

$$T_i = \int_{i-1998}^{i-1997} T(t)\,\mathrm{d}t. \tag{2.24}$$

The year for which the expected "treated incidence" is calculated corresponds to i and $t = 0$ corresponds to 1998, hence when $t = 1$ corresponds to 1999, $T_i = T_{1999}$. Annual incidence of first treatment contacts, given by the parameters in Table 2.1 and equation (2.24) are provided in Table 2.2.

$T(t)$	Exponential Model	Linear Model	Quadratic Model	Observed
Year i	Cases C. I.	Cases C. I.	Cases C. I.	Cases
1999	952 [789, 1131]	952 [786, 1111]	940 [851, 1030]	955
2000	912 [733, 1118]	915 [722, 1101]	922 [820, 1024]	899
2001	874 [681, 1106]	878 [659, 1090]	895 [773, 1016]	966
2002	837 [632, 1094]	841 [595, 1080]	858 [711, 1005]	858
2003	802 [587, 1082]	804 [531, 1070]	812 [634, 991]	861
2004	768 [545, 1070]	767 [468, 1059]	757 [541, 974]	704
2005	736 [506, 1058]	730 [404, 1049]	694 [432, 955]	774

Table 2.2: T_i, expected annual incidence of first treatment contacts with 95% confidence intervals when the parameters in Table 2.1, with equations (2.2), (2.3) and (2.4) substituted into equation (2.24).

From Table 2.2 it is evident that the number of first treatment contacts fluctuates over the seven year interval, however, overall, the number of first treatment contacts

decreases over this time period. The models selected to fit the data demonstrate a decrease in the incidence of first treatment contacts over the seven years, which is illustrated in Figure 2.2 below.
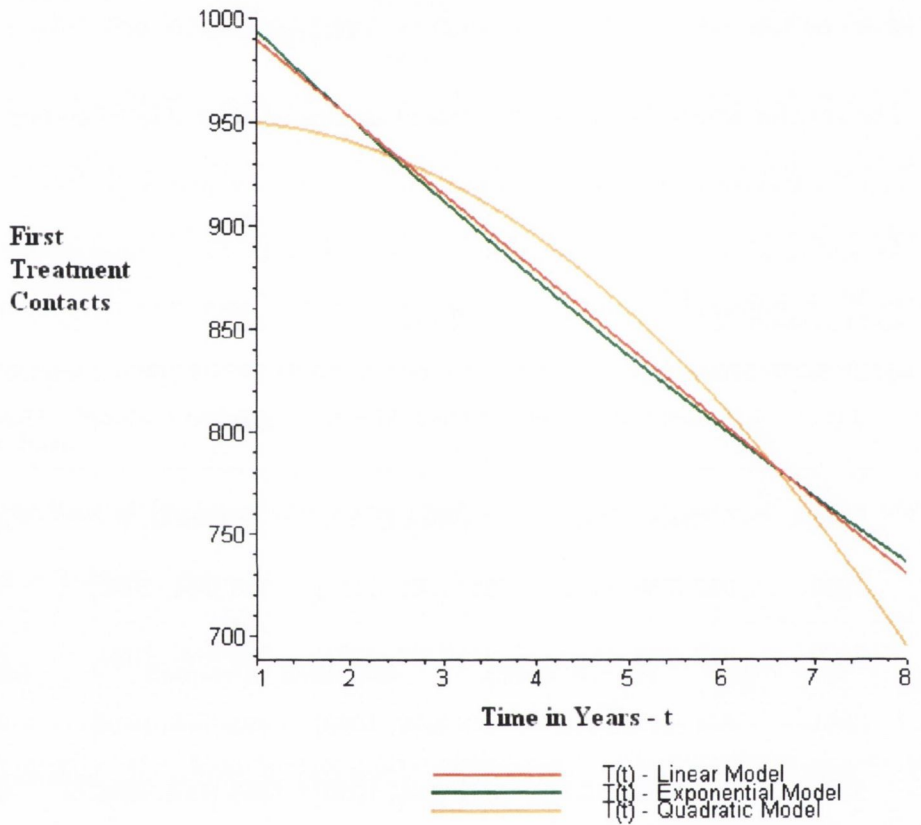
Figure 2.2: Graph of the incidence of first treatment contacts from 1999 to 2005 when $T(t)$ is described by equations (2.2), (2.3) and (2.4).

2.3.2 Results - The Rate of Progression to Treatment, f(t)

Since the exact rate of progression to treatment for opiate use is unknown, details from the (ROSIE) study are used to estimate $f(t)$ in equation (2.1) (Comiskey &

Cox 2007). The ROSIE study was the first national longitudinal prospective study of a cohort of over 400 opiate users entering treatment in 2003, which represented approximately 10% of all users who entered treatment that year. Comiskey & Cox (2007) found that the mean time between first opiate use and first treatment, for their sample of 322 individuals was 3.7 years with a standard deviation of 3.9. The time for progression to treatment ranged from zero to twenty-three years.

The parameters of the gamma distribution can be calculated, assuming that the time to treatment data of the ROSIE study follows a gamma distribution, the mean and variance of the data are used, to give,

$$\mu = 3.7 = \frac{\alpha}{\lambda} \text{ and } \sigma^2 = 15.21 = \frac{\alpha}{\lambda^2}. \tag{2.25}$$

Using equation (2.25) and some simple manipulation the following parameters are estimated for the gamma distribution, $\alpha = 0.90$ and $\lambda = 0.24$.

For ease of manipulation the parameters of the Weibull distribution are not estimated, instead the progression to treatment rates are examined when $\beta = 1$ and $\beta = 2$. The ρ parameter can then be calculated when $\beta = 1$ and $\beta = 2$ assuming the time to treatment data of the ROSIE study follows a Weibull distribution, the mean and variance are used to give,

$$\mu = 3.7 = \rho^{-1}\Gamma\left(1 + \frac{1}{\beta}\right) \text{ and } \sigma^2 = 15.21 = \rho^{-2}\Gamma\left(1 + \frac{2}{\beta}\right) - \mu^2. \tag{2.26}$$

The rates of progression to treatment with the Weibull distribution, denoted by $\omega(1, 0.27)$ and $\omega(2, 0.2395)$ are illustrated in Figure 2.3 below.

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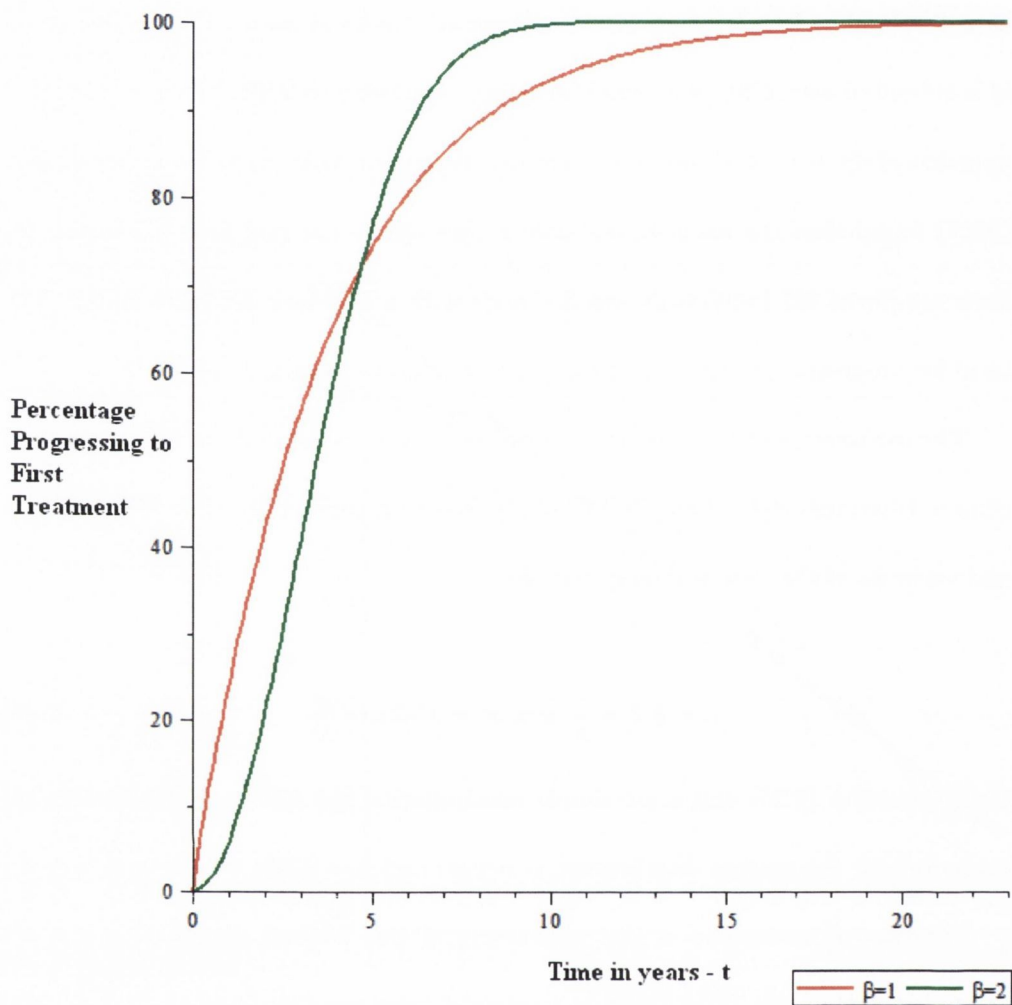
Figure 2.3: Graph of the cumulative Weibull distribution, when $\beta = 1$ and $\beta = 2$.

Figure 2.3 illustrates a rapid rate of progression to treatment initially for both $\beta = 1$ and $\beta = 2$. When $\beta = 2$ approximately 66% of contacts have commenced their first treatment episode within four years of commencing opiate use, with the over 90% of contacts progressing to treatment within seven years of initial opiate use. As a result the Weibull distribution with $\beta = 2$ is considered to model a rate of progression to treatment that is too fast to be applicable to the Irish setting.

A Weibull distribution with parameters $\beta = 1$ and $\rho = 0.27$ is considered to be

a better representation of the rate of progression to first treatment for the ROSIE study data. During the ROSIE study, Comiskey & Cox (2007) found that the maximum time clients used opiates before presenting for their first treatment episode was twenty three years, and while $\beta = 1$ progression to treatment is rapid within the first 10 years, the percentages entering first treatment using this model will decrease as time increases. It is evident from Figure 2.3 that this model does not demonstrate 100% treatment uptake by year twenty three of opiate use. Therefore a Weibull distribution with $\beta = 1$ and $\rho = 0.27$ is the best representation of the ROSIE study data as it accounts for the rapid progression to treatment within ten years for the majority of clients, representing the short incubation period. However this model also accounts for the small minority of opiate users with longer incubation periods.

2.3.3 Results - The Hidden, Untreated Incidence of Opiate Use, U(t)

The expected annual incidence of untreated opiate use denoted by U_i, can be estimated by integrating the rate of untreated opiate use, $U(t)$ in equations (2.10) and (2.17), when the rate of progression to treatment is described by a Gamma distribution, thus

$$U_i = \int_{i-1998}^{i-1997} U(t)\,\mathrm{d}t, \tag{2.27}$$

where time is measured in units of one year, with $t = 0$ corresponding to 1998. The expected annual incidence of hidden, untreated opiate use, U_i is estimated assuming the three forms of $T(t)$ in equations (2.2), (2.3) and (2.4) and the rate of progression to treatment having a Gamma distribution with parameters $\alpha = 1$ and

$\lambda = 0.27$ or $\alpha = 2$ and $\lambda = 0.54$. The values for U_i are given in the Tables 2.3 and 2.4 below.

It is possible to estimate U_i using all three models of $T(t)$ with the gamma distribution when $\alpha = 1$. However when the linear model of $T(t)$ is chosen in combination with the gamma distribution when $\alpha = 2$ it is not possible to estimate U_i, as this requires the second derivative of $T(t)$, which is equal to zero for the linear model.

$f(t)$	$\Gamma(1, 0.27)$ or $\omega(1, 0.27)$	$\Gamma(1, 0.27)$ or $\omega(1, 0.27)$	$\Gamma(1, 0.27)$ or $\omega(1, 0.27)$
$T(t)$	Exponential	Linear	Quadratic
Year (i)			
1999	801 [573, 1085]	815 [550, 1073]	890 [765, 1014]
2000	767 [532, 1073]	778 [486, 1062]	837 [676, 999]
2001	735 [494, 1061]	741 [423, 1052]	776 [572, 980]
2002	704 [459, 1049]	704 [359, 1041]	706 [453, 959]
2003	674 [426, 1038]	667 [295, 1031]	626 [318, 934]
2004	646 [396, 1027]	630 [232, 1021]	537 [168, 907]
2005	618 [367, 1015]	593 [168, 1010]	440 [2, 878]
Total	4944 [3247, 7347]	4926 [2513, 7290]	4812 [2953, 6670]

Table 2.3: U_i, expected annual incidence of hidden, untreated opiate use, with 95% confidence intervals, for $\Gamma(1, 0.27)$ and $\omega(1, 0.27)$ and $T(t)$ as in equations (2.2), (2.3) and (2.4).

$f(t)$	$\Gamma(2, 0.54)$	$\Gamma(2, 0.54)$
$T(t)$	Exponential	Quadratic
Year (i)		
1999	807 [588, 1085]	858 [711, 1005]
2000	773 [546, 1073]	806 [623, 989]
2001	740 [507, 1061]	745 [519, 970]
2002	709 [471, 1050]	674 [400, 949]
2003	679 [437, 1038]	595 [265, 925]
2004	651 [406, 1027]	506 [114, 898]
2005	623 [377, 1016]	408 [-51, 868]
Total	4981 [2953, 7350]	4593 [2581, 6604]

Table 2.4: U_i expected annual incidence of hidden, untreated opiate use, with 95% confidence intervals, for $\Gamma(2, 0.54)$ and $T(t)$, as in equations (2.2) and (2.4).

Following consultation with an expert in C++ (private communication, Dr. Conor Houghton, Department of Mathematics TCD, Spring 2010), the hidden, untreated incidence of opiate use was estimated using the C++ program when the rate of progression to treatment was described by a Weibull distribution with parameters $\beta = 2$ and $\rho = 0.24$. The integration is done on discrete time; this converts the equation into a matrix equation with a triangular matrix which is solved by an LU decomposition. The LU decomposition is a matrix decomposition which is a method used to factor a square matrix in a product of a lower triangular matrix and an upper triangular matrix. The lower triangular matrix only has zeros above the diagonal

and the upper triangular matrix only has zeros below the diagonal. The expected

annual incidence is illustrated in Figure 2.4 when the rate of first treatment contacts,

$T(t)$ is described by an exponential model.
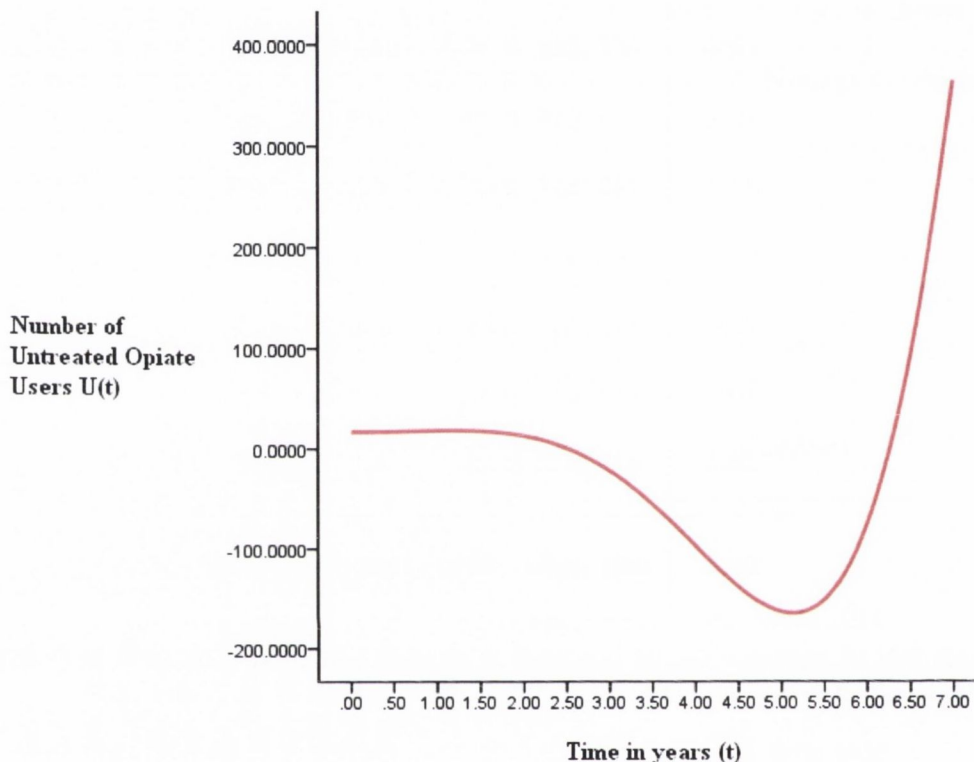
Figure 2.4: Incidence of untreated opiate use in Ireland from 1999 to 2005, when $T(t)$ is described by equation (2.2) and $f(t)$ is modelled using the Weibull distribution, equation (2.6).

The expected annual incidence is illustrated in Figure 2.5 below when the rate of

first treatment contacts, $T(t)$ is described by a quadratic model.
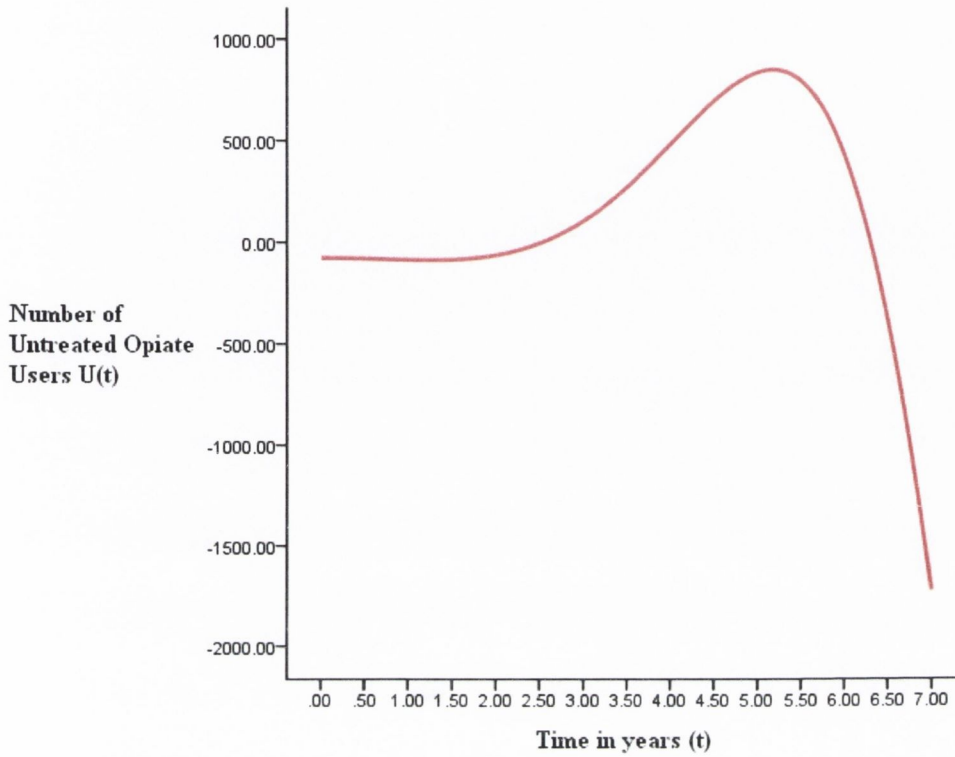
Figure 2.5: Incidence of untreated opiate use in Ireland from 1999 to 2005, when $T(t)$ is described by equation (2.4) and $f(t)$ is modelled using the Weibull distribution in equation (2.6).

An approximation of the incidence of untreated opiate use when the rate of progression to treatment is described by a Weibull distribution with parameters $\beta = 2$ and $\rho = 0.24$, is estimated by summing the areas of a collection of rectangles. The area under the curves in Figures 2.4 and 2.5 are divided into rectangles, where each rectangle estimated using the C++ program has width of 0.01 and a corresponding height which is the maximum value of the function. In order to estimate the incidence of opiate use in a year the area of all the rectangles in the interval are summed. The resulting incidence estimates are presented in Table 2.5.

$f(t)$	$\omega(2, 0.24)$	$\omega(2, 0.24)$
$T(t)$	Exponential	Quadratic
Year		
1999	17	-84
2000	16	-85
2001	-2	2
2002	-58	281
2003	-137	687
2004	-143	745
2005	106	-475
Total	-193	1054

Table 2.5: Expected annual incidence of hidden, untreated opiate use, for $\omega(2, 0.24)$ and $T(t)$, as in equations (2.2) and (2.4).

The estimates presented in Table 2.5 demonstrate a pattern of fluctuating incidence over the seven year period. As a result of the negative incidence estimates this model with a Weibull distribution, with parameters $\beta = 2$ and $\rho = 0.23$ is not deemed appropriate to estimate the hidden incidence of opiate use in an Irish setting. However the estimates must be viewed with caution in light of the fact that to date there has not been comprehensive research conducted on the exact rate of progression to first treatment for the Irish situation.

2.4 Conclusion and Discussion

The back calculation model has been analytically solved assuming a range of forms for the change in the treated incidence of drug use and the incubation period distribution. These new solutions have been applied to the problem of estimating the incidence of the hidden, untreated incidence of opiate use in Ireland from 1999 to 2005. From Tables 2.3 and 2.4 a pattern of decreasing hidden, untreated incidence of opiate use emerges regardless of the choice of parameters of the Gamma incubation period distribution and models for rate of first treatment contact. This departs from the findings of Comiskey & Ruskin (1992) in their application to HIV incidence and De Angelis *et al.* (2004) in their application to opiate incidence, both of whom noted that the predicted incidence depended more the choice of incubation period rather than on the choice of treated incidence.

It is not strictly possible to validate the estimates of the incidence of untreated opiate use as there are no published Irish incidence estimates to date. Whilst estimates are based on a comprehensive national treatment evaluation study and data from the national treatment reporting system, further research is required to produce more reliable estimates of the untreated incidence of opiate use in Ireland. The estimates produced must be viewed with caution in light of the fact that, as yet, little is known about the exact rate of progression to first treatment for opiate use in Ireland. Further research into modelling the exact rate of progression to treatment is essential in order to produce more consistent incidence estimates. This is attempted in Chapter 3.

2.5   Chapter Summary

In this chapter the back calculation model has been solved in order estimate the hidden, untreated incidence of opiate use. The solutions have been implemented to produce estimates of the hidden, untreated incidence of opiate use in Ireland from 1999 to 2005 when the exact rate of progression to first treatment for opiate use is unknown. In the following chapter, data on times to first treatment for opiate use will be examined with a view to modelling for the first time in Ireland the exact rate of progression to treatment in order to obtain more accurate incidence estimates.

Chapter 3

Modelling the Rate of Progression to First Treatment for Opiate Use

3.1 Introduction

In the previous chapter the back calculation model was developed to produce esti-mates of the incidence of untreated opiate use in Ireland. The time to treatment is an important element of the back calculation model and the mean time to treatment was previously taken from the ROSIE study and applied to the model to produce analytical solutions to the model. Isham (1989), Comiskey & Ruskin (1992) and De Angelis *et al.* (2004) noted that the choice of incubation period distribution was sig-nificant when predicting incidence however little is known about the true incubation period from first opiate use to first treatment for use. Whilst the estimate of time to treatment was taken from a comprehensive national treatment evaluation, further research on rates of progression to treatment would be beneficial to obtain more exact incidence estimates. The progression to treatment is defined as the length of time between an individual commencing opiate use and progressing to first treat-ment and is denoted by $f(t)$. The National Drug Strategy Interim report 2009 to 2016 identifies a problem with drug users gaining prompt access to treatment and

one of the key performance indicators mentioned in the report is 100% access to treatment within one week of assessment for individuals under eighteen and within one month of assessment for those over eighteen (Department of Community, Rural and Gaeltacht Affairs 2009). It is essential for treatment service providers to be aware of the rates of progression to treatment for all drug users and modelling this would enable treatment service providers to meet the key indicators mentioned above. The specific aim of this chapter is;

- To derive a model for the rate of progression to first treatment for opiate use, to enable service providers to provide adequate treatment program and facilities for future service users.

3.2 Modelling the Incubation Period of Infectious Disease

Modelling the incubation period of infectious disease can be dated back to 1546, when the incubation period of rabies was documented by the Italian physician Girolamo Fracastro (1478-1553) (Fracastorii 1930), as cited by Nishiura (2007). Following on from the pioneering work of Fracastro, considerable attention has been paid to the problem of modelling the incubation period of infectious diseases such as measles, poliomyelitis, smallpox and SARS (Nishiura 2007, Farewell *et al.* 2005). As some of the characteristics of infectious diseases such as their hidden nature prior to the onset of symptoms, are similar to those of problem drug use, it may be appropriate to apply the models for the incubation period of disease to the times to first treatment for opiate use.

As the mathematical model for which the incubation period, $f(t)$, is being mod-

elled for is from AIDS epidemiology it is appropriate to examine the incubation period models from HIV and AIDS. This will form a starting point for modelling the rate of progression to treatment for opiate use. A wide range of research has been carried out in the past on the incubation period distribution of HIV and AIDS. Blythe & Anderson (1988) defined the incubation period distribution of AIDS as the time from first infection with HIV to the appearance of symptoms of the disease AIDS. The AIDS incubation period varied depending on the mode of transmission of the disease such as blood transfusion, sexual intercourse or intravenous drug abuse. According to Medley *et al.* (1988) the incubation period of AIDS is both long and variable however the authors also noted that data on the AIDS incubation period is difficult to obtain.

Kuo *et al.* (1991) conducted a study using the CDC (Centre for Disease Control) published rates of progression from the HIV infection to AIDS. The date of infection with HIV is generally unknown with the exception of transfusion associated AIDS cases therefore the sample is truncated and biased, as it excludes individuals with a short incubation period, those whom might have enrolled in the study but whom develop AIDS before the enrolment date. The incubation period of transfusion related AIDS cases can be definitively ascertained due the availability of the date of exposure to infection and AIDS diagnosis date.

The Gamma and Weibull distributions have been widely used in the past to model the incubation periods of disease (Anderson & Medley 1988, Medley *et al.* 1988). Isham (1989) and Kuo *et al.* (1991) applied these distributions when modelling the AIDS incubation period. Blythe & Anderson (1988) noted that when chosing one of the various probability distributions to model the incubation period

of a disease one must consider the overall aim of the mathematical model and which of the distributions is of greatest utility in the model. According to Kuo *et al.* (1991) in order to project future numbers of AIDS cases a previous knowledge of the incubation period distribution is vital.

In more recent times the Gamma and Weibull distributions have been applied to the problem of modelling the latency period of problem drug use in London, The Netherlands, Italy and Portugal (Rossi 1999). Rossi (1999) defined the latency period of problem drug use as the time from first heroin use and first treatment demand. The knowledge gained from studies on HIV and AIDS incubation period distribution models could be applied to the problem of modelling the progression to treatment for drug use.

3.3   Methodology

For the purpose of this study it is considered possible to model the rate of progression to first treatment for opiate use in a similar way to the incubation period of infectious disease. It is plausible to treat the rate of progression to treatment for opiate use in a similar manner to the incubation period of a disease, as knowledge of the incubation period in both situations is relevant to the prevention and control of infectious disease and illegal opiate use. It is of particular interest to assess if any of the models used to describe the incubation period of disease are applicable to the problem of modelling the rate of progression to treatment for opiate use. In this chapter the known times to first treatment for opiate users are studied to ascertain if the times follow a particular pattern which could be modelled. It would then be possible to predict future numbers of first treatment contacts using the model. With

this in mind some techniques for fitting incubation period models to data on times
to progression to treatment are evaluated in the following sections.

3.3.1   Probability Density Function

Probability density functions have primarily been used to model the incubation
period distribution of infectious diseases. Probability density functions are investi-
gated as a means of modelling the rate of progression to first treatment for opiate
use. The probability density function of a continuous random variable is a function
which can be integrated to find the probability that a random variable takes a value
in a given interval. The probability density function of a continuous random variable
is denoted by $f(t)$, which satisfies the following properties;

$$f(t) \geq 0,$$

$$\int_0^\infty f(t) \, \mathrm{d}t = 1. \tag{3.1}$$

$$P(a \leq t \leq b) = \int_a^b f(t) \, \mathrm{d}t$$

In terms of drug use the probability density function is used to find the probability
that a drug user will progress to treatment within a given time interval. We are
interested in studying the probability that an opiate user will progress to first treat-
ment within a given time interval. The probability density functions for the Gamma
and Weibull distributions are presented in the following sections.

3.3.2   The Gamma and Weibull Distributions.

The Gamma and Weibull probability distributions were chosen to model the rate of
progression to treatment for opiate use. These models are plausible for describing
the rate of progression to treatment as both are used to measure time to failure, i.e.
time from first opiate use to the time when an individual fails to be an untreated

opiate user (the individual presents for treatment).

As seen in chapter 2, the Gamma distribution is denoted by $\Gamma(\alpha, \lambda)$ and has the probability density function, defined by $f(t)$ where $f(t)$ is the probability that a random variable takes a value in a given interval and is given by equation (3.2) below,

$$f(t) = \frac{\lambda(\lambda t)^{\alpha-1} \exp(-\lambda t)}{\Gamma(\alpha)}, \tag{3.2}$$

with $t = 0$ and mean, $\mu = \frac{\alpha}{\lambda}$. The shape and scale parameters are α and λ respectively. The shape parameter affects the shape of the distribution and the scale parameter affects the dispersion of the distribution. The effects of changing the shape parameter of a Gamma distribution is illustrated in Figure 3.1.
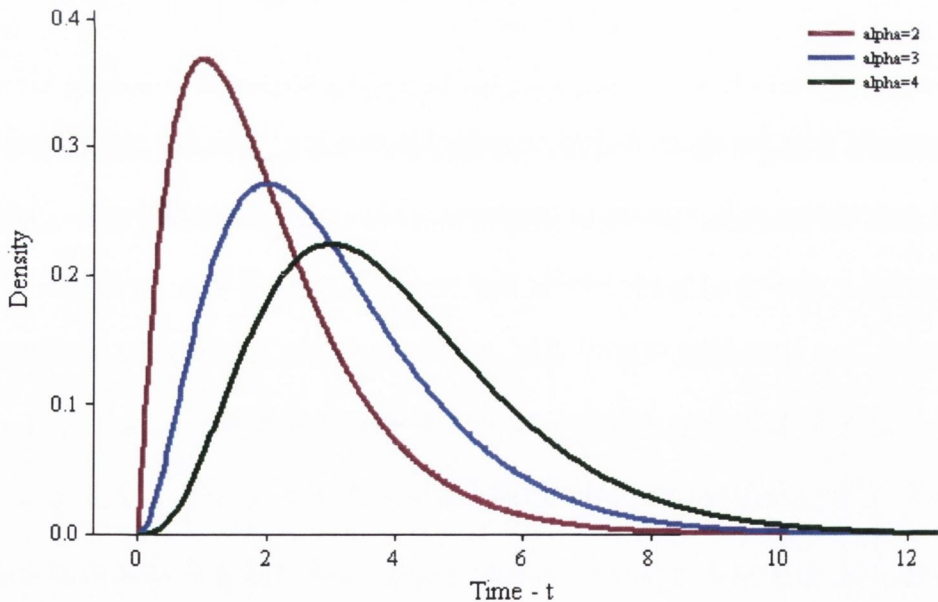
Figure 3.1: Gamma probability density with shape parameter, $\alpha = 2$, $\alpha = 3$ and $\alpha = 4$ and scale $\lambda = 1$.

As we have seen the Weibull distribution is denoted by $\omega(\beta, \rho)$ and has the probability density function, $f(t)$, where $f(t)$ again describes the probability that a random variable takes a value in a given interval and is given by equation (3.3) below.

$$f(t) = \beta\rho(\rho t)^{\beta-1}exp\{-(\rho t)^{\beta}\}, \tag{3.3}$$

for $t \geq 0$ and mean, $\mu = \rho^{-1}\Gamma\left(1 + \frac{1}{\beta}\right)$. The shape and scale parameters are β and ρ respectively. The shape parameter depicts the shape of the Weibull distribution curve and the scale describes the position of the curve relative to the threshold value. The threshold value is the earliest time a failure may occur and locates the distribution along the time scale. The effects of changing the shape parameter of a Weibull distribution is illustrated in Figure 3.2.

3.3.3 Probability Plots

Probability plots are a graphical technique to assess if data can be modelled using a particular distribution (Chambers *et al.* 1983). For example the probability plot can be used to assess if the Gamma or Weibull distributions fit data on time to first opiate treatment. The method of probability plotting takes the cumulative distribution function of the distribution and attempts to linearise using specially constructed paper. The cumulative distribution and the associated confidence intervals are calculated based on the parameters estimated from the data. If the data comes from the theoretical distribution the plotted percentile points will follow an approximate straight line (Upton & Cook 2002).
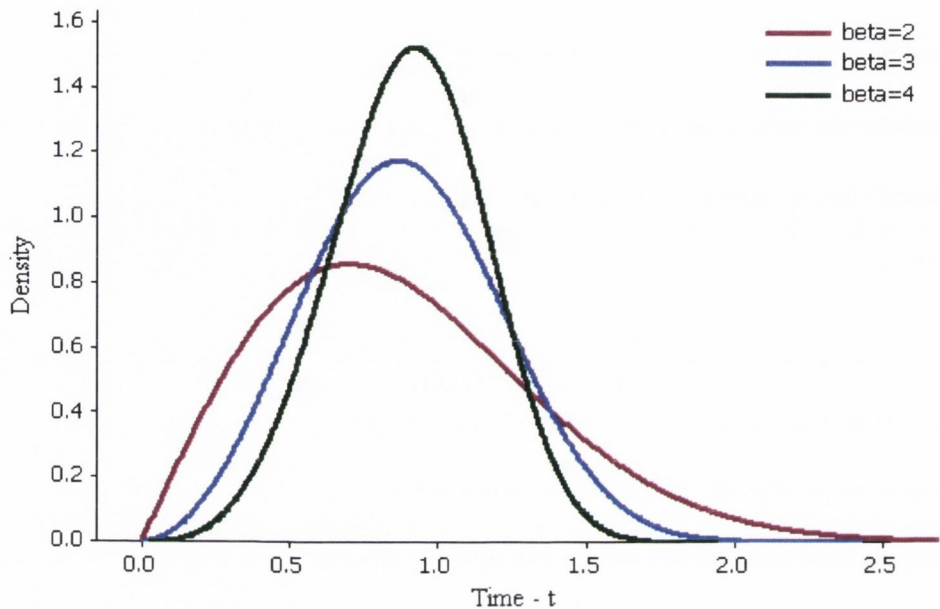
Figure 3.2: Weibull probability density curve with shape parameter, $\beta = 2$, $\beta = 3$ and $\beta = 4$ and scale, $\rho = 1$.

3.3.4 The Method of Moments

Another technique to fit a distribution to the observed data is the Method of Moments as it is used to estimate the parameters of a distribution. Using this technique estimates of the required parameters can be determined by equating sample moments which can then be matched with the corresponding distribution moments. The first moment is the expected value, of a random variable with a Gamma distribution and is given by,

$$E_{\alpha,\lambda}(X) = \frac{\alpha}{\lambda}. \tag{3.4}$$

where $X_1, ..., X_{5,022}$ are the 5,022 times to first treatment for opiate use. The second moment is the expected value of its square

$$E_{\alpha,\lambda}(X^2) = \frac{\alpha(\alpha+1)}{\lambda^2}. \tag{3.5}$$

The method of moments estimator solves

$$\bar{X} - \frac{\hat{\alpha}}{\hat{\lambda}} = 0$$

$$\frac{1}{n}\sum_{i=1}^{n} X_i^2 - \frac{\hat{\alpha}(\hat{\alpha}+1)}{\hat{\lambda}^2} = 0 \tag{3.6}$$

which yields estimates of the population parameters α and λ, given by:

$$\hat{\lambda} = \frac{\bar{X}}{\frac{1}{n}\sum_{i=1}^{n} X_i^2 - \bar{X}^2} \tag{3.7}$$

and

$$\hat{\alpha} = \bar{X}\hat{\lambda} = \frac{\bar{X}^2}{\frac{1}{n}\sum_{i=1}^{n} X_i^2 - \bar{X}^2}, \tag{3.8}$$

The method of moments is quick and easy to implement by hand and produces asymptotically unbiased estimators. An asymptotically unbiased estimator is an estimator which tends to be unbiased as the sample number increases.

In the following section the method of moments and probability plots will be applied to the first treatment data. Using these methods it is possible to ascertain if the Gamma and Weibull distributions are adequate models for describing progression to first treatment for opiate use.

3.4 Data

Data on times to first treatment for opiate use were analysed for the years 1999 to 2005. Dr Jean Long from the Health Research Board (HRB) provided data on the numbers progressing to first treatment and the length of time clients used opiates before entering first treatment grouped in yearly intervals, i.e. less than twelve months, twelve to twenty three months and twenty-four to thirty-five months, etc. Dr Long kindly compiled this data using the National Drug Treatment Reporting System (NDTRS). The reporting system was originally established in 1990 as an epidemiological database on treated drug use in the greater Dublin area and was later extended to cover all areas of Ireland (Alcohol and Drug Research Unit of the Health Research Board 2007). The reporting system was originally developed in line with the Pompidou Groups definitive protocol. The Pompidou Group is an intergovernmental body which provides a multidisciplinary forum at the European level where ideas and information on drug misuse and trafficking problems are exchanged by experts. The reporting system was later changed in line with the European Monitoring Centre for Drugs and Drug Addictions Treatment Demand Indicator. Data is submitted to the National Drug Treatment Reporting System from outpatient facilities, general practitioners and low threshold services and provides a comprehensive list of treatment data. In 2004, 563 services and general practitioners were requested to participate in data collection, the data is anonymous as the clients name does not appear on the form; however service providers collecting data endeavour to ascertain a full and accurate client history and to establish if the client is new or was previously treated.

Over the seven year period from 1999 to 2005, 6,017 individuals began their first treatment episode for opiate use. Table 3.1 below illustrates an overall reduction in the numbers progressing to treatment between 1999 and 2005. However the number of individuals entering their first treatment episode increases and decreases from year to year which may indicate fluctuations in the number of treatment places available. Availability of treatment places may vary in response to changes in funding or may be related to the number treatment places available after clients receiving their second or subsequent treatment. The lowest number of clients entering their first treatment episode was recorded in 2004, with only 704 contacts compared with 2001 which had the highest number of first treatment contacts for opiate use with 966 individuals entering their first treatment episode. Analysis showed that the mean number of clients entering first treatment over the seven year period was 860 with the 95% confidence interval [772, 947] and standard deviation 94.4.

Year Entered First Treatment	1999	2000	2001	2002	2003	2004	2005	1999-2005 (%)
Length of Time Using Opiates								
Less than 12 months	88	80	97	77	77	46	72	537 (**8.92**)
12 to 23 months	120	73	133	95	101	72	89	683 (**11.35**)
24 to 35 months	146	116	106	108	90	91	74	731 (**12.15**)
36 to 47 months	137	104	103	93	74	69	56	636 (**10.57**)
48 to 59 months	113	128	102	87	65	49	64	608 (**10.10**)
60 to 71 months	79	116	81	66	65	31	42	480 (**7.98**)
72 to 83 months	61	77	74	70	66	40	29	417 (**6.93**)
84 to 95 months	29	38	57	56	43	39	34	296 (**4.92**)
96 to 107 months	31	33	38	43	40	44	37	266 (**4.42**)
108 to 119 months	20	22	32	28	48	20	35	205 (**3.41**)
120 to 131 months	10	16	20	20	28	32	37	163 (**2.71**)
132 months or more	63	57	71	64	110	95	148	608 (**10.10**)
Data not recorded	58	39	52	51	54	76	57	387 (**6.43**)
Total	955	899	966	858	861	704	774	6017 (**100**)

Table 3.1: The numbers entering treatment per year and the lengths of time using opiates before entering treatment.
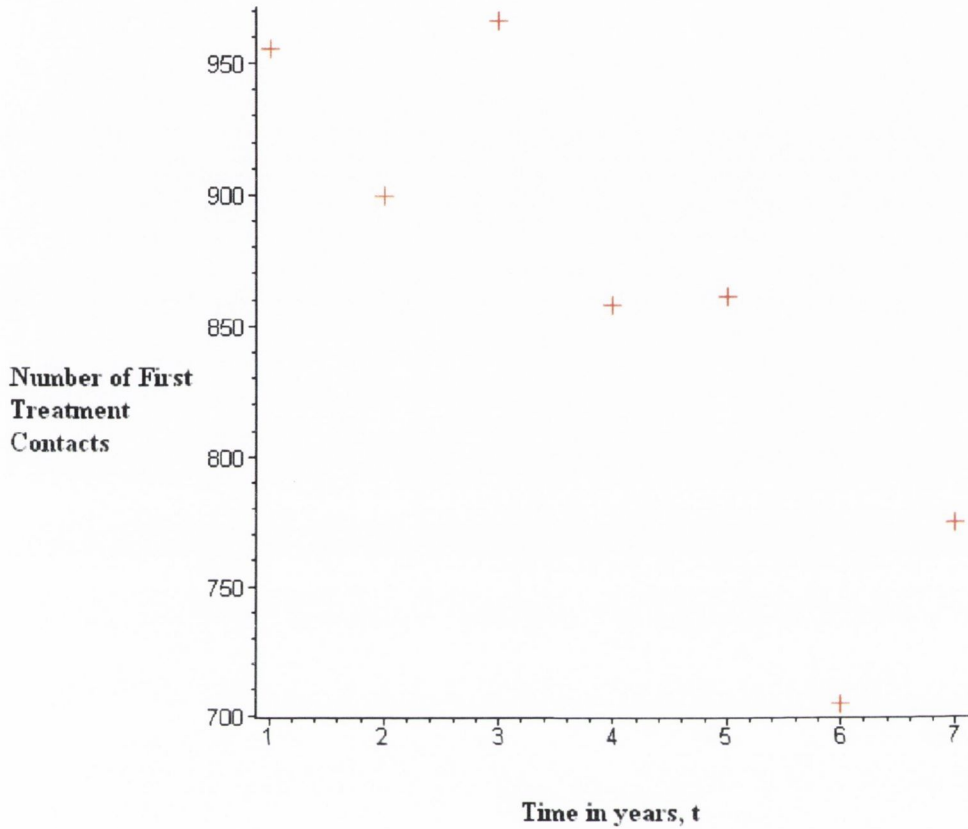
Figure 3.3: Observed first treatment contacts in Ireland 1999 to 2005, corresponding to $t = 1$ to $t = 7$.

Further data analysis included only data on clients for whom the lengths of time using opiates before entering treatment were documented. There was no data recorded on the length of time between first opiate use and commencing treatment for 387 of the 6,017 clients entering first treatment between 1999 and 2005. For 608 of the contacts that entered first treatment the period of use was in excess of 132 months, as there was no upper bound on the number of months recorded these clients were excluded from the analysis on the times of progression to first treatment.

For the purpose of analysis the midpoint of the class interval was considered. For each year the mean number of years an individual uses opiates for before entering first treatment with standard deviation and 95% confidence interval were estimated.

All data over the seven year period for each class interval were combined and analysed to calculate the overall mean with standard deviation and the 95% confidence interval. Table 3.2 illustrates that the annual mean time a client used opiates for before progressing to treatment ranged from 3.82 years with a standard deviation of 2.39 to 4.58 years with standard deviation 2.98. The 95% confidence intervals were [3.66, 3.98] and [4.33, 4.84] respectively. The mean of the combined data is 4.3 years with standard deviation 2.76 and the 95% confidence interval [4.22, 4.37].

Year	Mean	Standard Deviation	95% C.I.
1999	3.82	2.39	[3.66, 3.98]
2000	4.31	2.47	[4.14, 4.48]
2001	4.18	2.72	[4.00, 4.63]
2002	4.37	2.74	[4.17, 4.57]
2003	4.54	2.97	[4.32, 4.76]
2004	4.58	2.98	[4.33, 4.84]
2005	4.48	3.13	[4.22, 4.74]
1999-2005	4.30	2.76	[4.22, 4.37]

Table 3.2: The mean number of years using opiates before progressing to first treatment.

The relative frequency for the rate of progression to treatment is the proportion of

individuals who present for first treatment for opiate use having used opiates for a certain period of time. The relative frequencies were calculated using,

$$rfn(E) = \frac{r}{n} \tag{3.9}$$

were r is the number of clients presenting for first treatment in a certain class interval and n is the total number of first treatment contacts for opiate use in a given period of time. The relative frequencies of rates of progression to first treatment for opiate use can be observed in Figure 3.4 below.
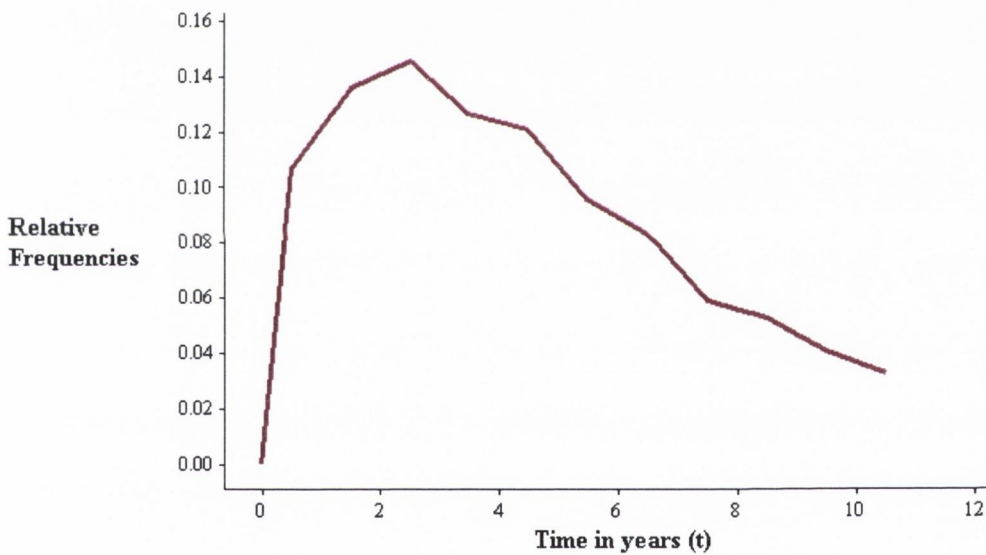
Figure 3.4: Relative frequencies of times to first treatment for opiate use in Ireland, 1999-2005.

Figure 3.5 illustrates that over 50% of contacts enter their initial treatment episode within four years of first using opiates. The rate of progression to treatment is relatively short with 11% of contacts over the seven year period entering their first treatment episode in less than twelve months after initial opiate use. The percentage

of first treatment contacts decreases steadily as the rate of progression to treatment increases after four years.
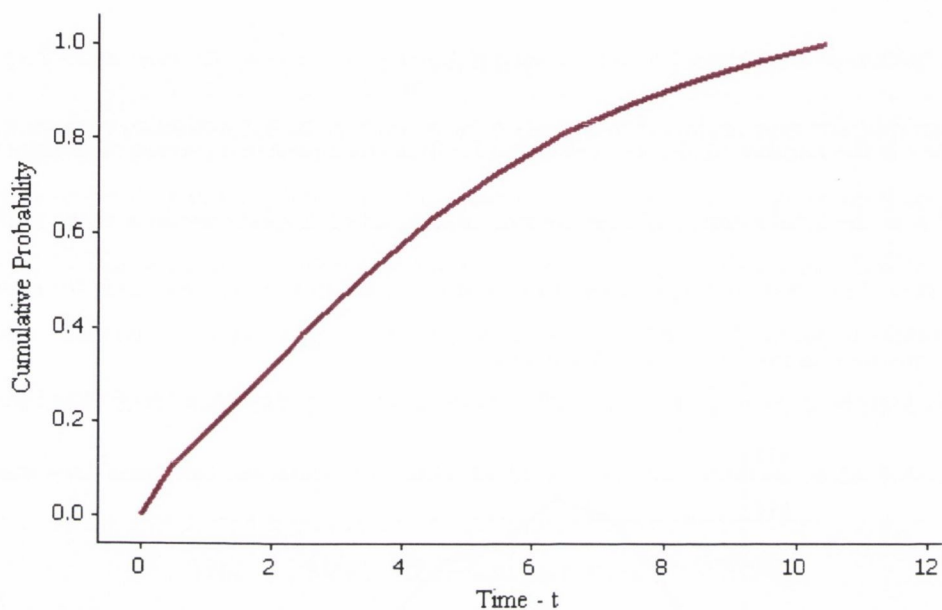
Figure 3.5: Cumulative frequencies of times to first treatment for opiate use in Ireland, 1999-2005.

The Gamma and Weibull distributions described in Section 3.3.2 were fitted to this data with the aim of finding an appropriate distribution and parameters to represent the data.

3.5 Results

The mean time of progression to treatment for opiate use of 4.3 years is very short in comparison to other European cities. The EMCDDA (2000) analysed data to estimate the latency period of heroin users, the time between first heroin use and first treatment demand, of a selection of European cities, namely Rome, London, Amsterdam and the French Community of Belgium and Lisbon. The authors estimated

latency periods of of 6.7, 7.0, 7.1, 7.1 and 8.7 respectively. However the EMCDDA (2000) also estimated the latency period for Dublin to be 3.1 years and discussed the lack of available data as a limitation which may explain the short latency period recorded. The finding of 4.3 years is in line with the EMCDDA's finding of 3.1 years as all opiate users not just heroin users are considered for this study and data is available for a seven year period.

3.5.1 Results: Fitting the Weibull Distribution to the Data

The statistical package Minitab was used to fit a Weibull distribution to the interval censored data on times to progression to treatment. As the data on times to treatment were interval censored, Minitab estimates the cumulative probabilities using the Turnbull method (Turnbull 1976). Turnbull's method is a nonparametric maximum likelihood estimator of the distribution function of X, $F(t)$. The probability plots and correlation coefficients estimated by Minitab were used to ascertain if the Weibull distribution fits the observed data. Both the least squares and maximum likelihood estimation techniques are options which could be chosen to estimate the distribution parameters. The Weibull probability plots using both of the parameter estimation techniques mentioned are displayed in Figures 3.6 and 3.7 below.
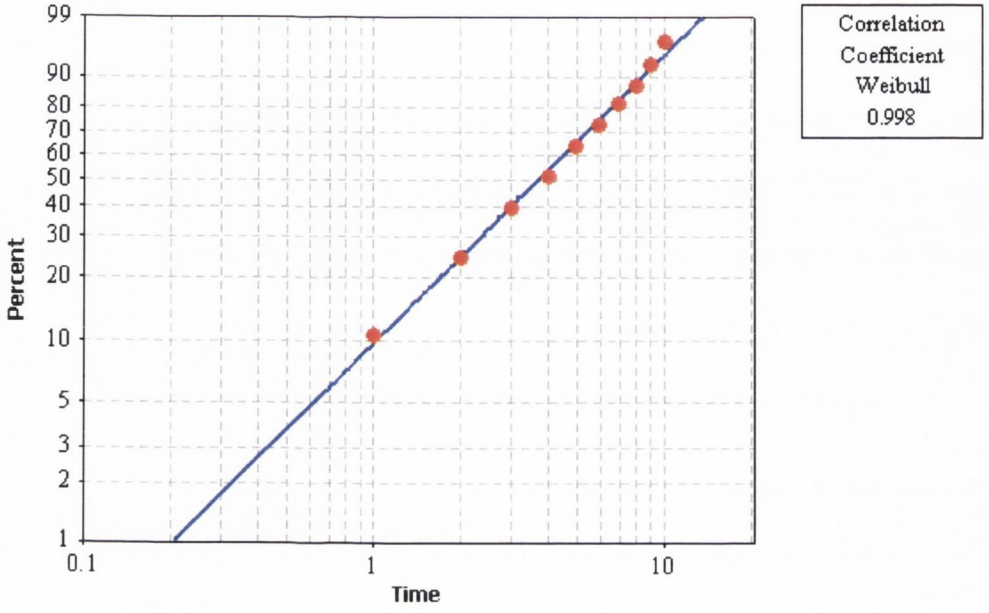
Figure 3.6: Weibull probability plot - least squares method.
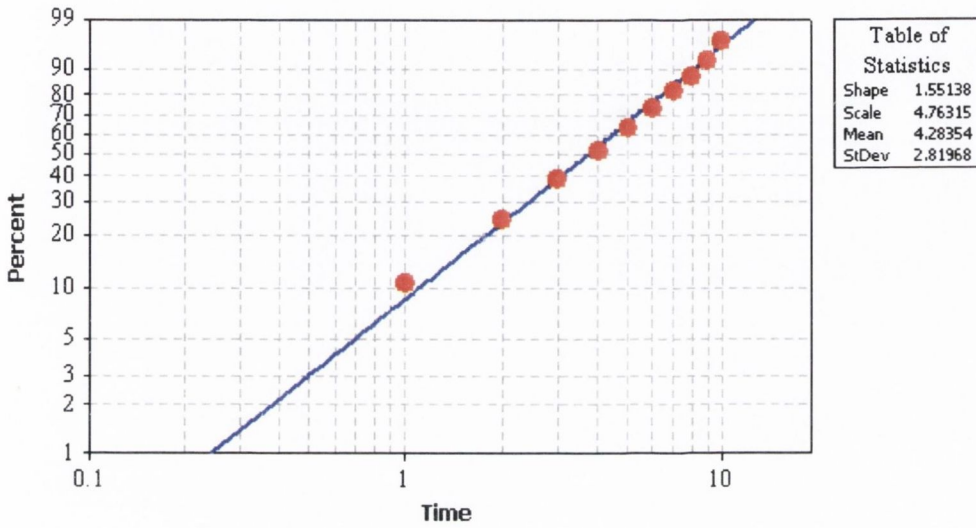
Figure 3.7: Weibull probability plot - maximum likelihood method.

It can be observed from the probability plots in Figures 3.6 and 3.7 that the plot percentile points follow an approximate straight line and therefore the plotted points fall very close to the distribution line. The output in Figure 3.6 displays a correlation coefficient of 0.998, which is very close to one and indicates a very good fit. The R^2 value of 0.996 implies that 99.6% of the variation in the observations is explained by the model. Therefore the Weibull distribution is a suitable choice when modelling the data on progression to first treatment for opiate use.

The data on progression to first treatment can be modelled using a Weibull distribution with $\beta = 1.55$ with a 95 % confidence interval of [1.52, 1.58] and $\rho = 0.21$. The mean of the Weibull distribution is 4.28 with a standard deviation of 2.82, which illustrates only a slight deviation from the mean and standard deviation of the raw data as displayed in Table 3.2. Figure 3.8 shows the observed progression

to treatment and the Weibull distribution which was fitted to the data.
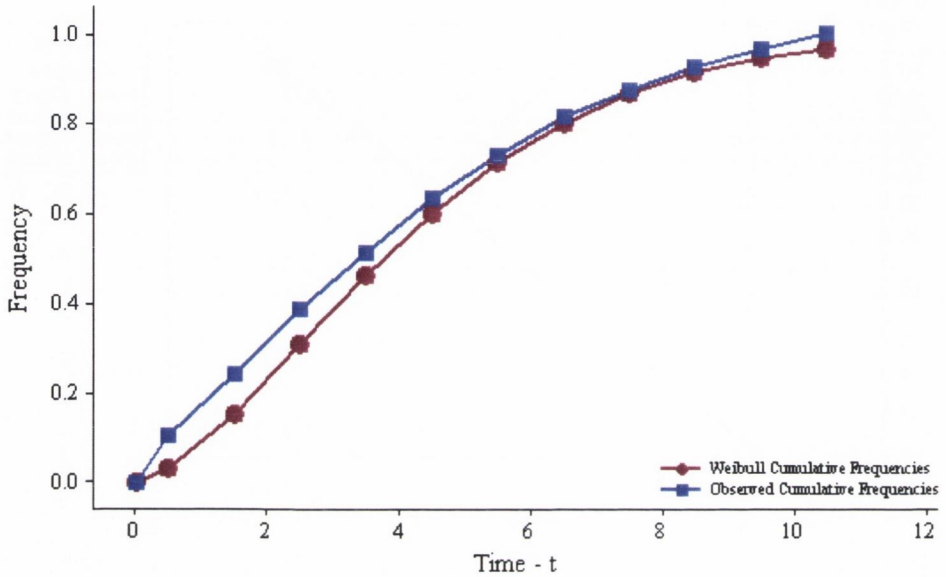
Figure 3.8: Observed cumulative frequencies of times to first treatment for opiate use and cumulative Weibull probability distribution fitted to data on times to first treatment for opiate use.

The Weibull cumulative distribution graph suggests that half of first treatment contacts have entered first treatment within four years and 60% of contacts a have entered treatment within four and a half years of commencing opiate use.

3.5.2 Results: Fitting the Gamma Distribution to the Data

It is not possible to use the statistical package Minitab to fit a Gamma probability plot to interval censored data. Therefore the parameters of the Gamma distribution are estimated using the method of moments described in Section 3.3.4. Using that method the following parameters were estimated for the Gamma distribution, $\alpha = 2.46$ and $\lambda = 0.57$. Figure 3.9 shows the observed progression to treatment and the Gamma distribution with parameters $\alpha = 2.46$ and $\lambda = 0.57$, which was fitted to

the data.
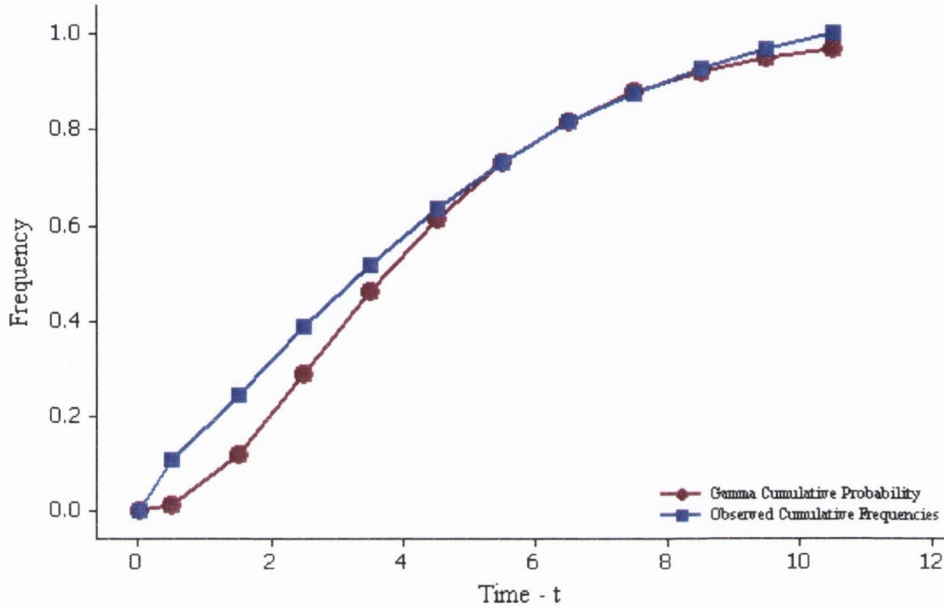
Figure 3.9: Observed cumulative frequencies of times to first treatment for opiate use and cumulative Gamma probability distribution fitted to data on times to first treatment for opiate use.

Figure 3.9 illustrates a rapid rate of progression to treatment for opiate use in the Irish setting, with over half of first treatment contacts made within the first five years of opiate use and almost 100% of clients entering first treatment within ten years of initial opiate use.

3.6 Conclusions and Discussions

The Gamma and the Weibull distributions have been fitted to the NDTRS data on time to first treatment for opiate use. Both of the distributions have been deemed appropriate for modelling the rate of progression to treatment. These models will aid treatment providers to fulfill one of the overall strategic aims of the National

Drug Strategy 2009-2016 of providing opiate users with appropriate and timely access to treatment and rehabilitation services as it will enable them to anticipate when the need will arise. The next chapter utilises the parameter estimates for the distributions in combination with the back calculation model to obtain estimates of the hidden, untreated opiate use in Ireland.

3.7   Chapter Summary

Models have been fitted to data on the times to first treatment for opiate use, known as the latency period. The next chapter uses some of the models fitted to the data along with the back calculation model and the known rates of first treatment incidence as outlined in chapter 2 in order to estimate the incidence of untreated opiate use.

Chapter 4

Estimates of the Incidence of Untreated Opiate Use when the Exact Rate of Progression to Treatment is Known

4.1 Introduction

The back calculation method was employed in chapter 2, to produce the first estimates of the hidden, untreated incidence of opiate use. These estimates were obtained by applying the known rate of first treatment contacts and estimating the rate of progression to treatment from the known mean time to first treatment for opiate use.

With the exception of work by EMCDDA (2000), little has been done to model the rate of progression to first treatment for opiate use internationally and in Ireland, this may be due to the lack of appropriate models so far and the lack of published data available on times to progression to treatment to date as a result of the hidden nature of drug use. It can be seen from chapter 3, that data on times to first treatment were requested from the Health Research Board and for the first time in Ireland, grouped data on times to treatment were made available for this study.

In the previous chapter incubation period models were fitted to the data. The specific aims of this chapter are:

- To implement the incubation period models fitted to the data in chapter 3 into the integral equation for the back calculation model.

- To improve the incidence estimates produced in chapter 2 by implementing the exact distribution chosen to model the rate of progression to first treatment.

4.2   Methodology

The back calculation equation (4.1), as we have seen in Chapter 2, is a linear Volterra equation of the first kind with a difference kernel and can be expressed as

$$T(t) = \int_0^t U(t-u)f(u)\,\mathrm{d}u. \tag{4.1}$$

Using equation (4.1) it is possible to determine the number of untreated users opiate at a specific time by combining knowledge of the known number of first treatments and the known times to first treatments for opiate users. Equation (4.1) may be viewed as a convolution of $U(t)$ and $f(t)$, however it is not possible to find an analytical solution by means of a simple inverse Laplace Transform when the chosen model of $f(t)$ is given by a Gamma distribution with $\alpha \in \mathbb{R}$ (Comiskey 1992). In order to find a solution to equation (4.1) the equation can be changed by differentiating into a generalized Abel integral equation. The solution of this equation is then given in the terms of an integral in the two known functions $T(t)$ and $f(t)$.

Equation (3.2) from Chapter 3, which is given by,

$$f(u) = \frac{\lambda(\lambda(u))^{\alpha-1}\exp(-\lambda(u))}{\Gamma(\alpha)}, \tag{4.2}$$

with $2 \leq \alpha \leq 3$ is substituted into equation (4.1) and the change of variables $s = t-u$ is made to give,

$$T(t) = \int_0^t U(s)\frac{\lambda(\lambda(t-s))^{\alpha-1}exp(-\lambda(t-s))}{\Gamma(\alpha)}\,\mathrm{d}s. \tag{4.3}$$

Leibnitz rule for differentiating an integral is used to differentiate equation (4.3) with respect to t and this is then rearranged to give:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = -\lambda T(t) + \int_0^t U(s)\frac{\lambda^\alpha}{\Gamma(\alpha)}(\alpha-1)(t-s)^{\alpha-2}\exp(-\lambda(t-s))\,\mathrm{d}s. \tag{4.4}$$

Equation (4.4) is differentiated with respect to t and rearranged to give,

$$\frac{\mathrm{d}^2T}{\mathrm{d}t^2} + 2\lambda\frac{\mathrm{d}T}{\mathrm{d}t} + \lambda^2 T(t) = \int_0^t U(s)\frac{\lambda^\alpha}{\Gamma(\alpha)}(\alpha-2)(\alpha-1)(t-s)^{\alpha-3}\exp(-\lambda(t-s))\,\mathrm{d}s. \tag{4.5}$$

Equation (4.5) is rearranged to give,

$$\frac{\mathrm{d}^2T}{\mathrm{d}t^2} + 2\lambda\frac{\mathrm{d}T}{\mathrm{d}t} + \lambda^2 T(t) = \frac{\lambda^\alpha}{\Gamma(\alpha)}(\alpha-2)(\alpha-1)\exp(-\lambda t)\int_0^t U(s)(t-s)^{\alpha-3}\exp(\lambda s)\,\mathrm{d}s. \tag{4.6}$$

Let $C = \dfrac{\Gamma(\alpha)}{\lambda^\alpha(\alpha-1)(\alpha-2)}$ and $\alpha - 3 = -p$ to get,

$$C\exp(\lambda t)\left(\frac{\mathrm{d}^2T}{\mathrm{d}t^2} + 2\lambda\frac{\mathrm{d}T}{\mathrm{d}t} + \lambda^2 T(t)\right) = \int_0^t U(s)(t-s)^{-p}\exp(\lambda s)\,\mathrm{d}s, \tag{4.7}$$

where $0 < p < 1$. Equation (4.7) is in the form of a generalized Abel equation:

$$F(t) = \int_0^t \frac{\tilde{U}(s)}{(t-s)^p} \, ds, \tag{4.8}$$

with $\tilde{U}(s)$ as the required unknown. The solution to the generalized Abel equation, (4.8) which is outlined by Jerri (1985) is given by:

$$U(t) = \frac{\sin(p\pi)}{\pi} \frac{d}{dt} \int_0^t (t-s)^{p-1} F(s) \, ds. \tag{4.9}$$

In equation (4.7), $\tilde{U}(s) = U(s)e^{\lambda s}$ is the unknown. The solution to equation (4.7) is given by,

$$U(t) = \frac{\sin(p\pi)}{\pi} \exp(-\lambda t) \frac{d}{dt} \int_0^t (t-s)^{p-1} F(s) \, ds. \tag{4.10}$$

where

$$F(s) = C \exp(\lambda s) \left(\frac{d^2 T}{ds^2} + 2\lambda \frac{dT}{ds} + \lambda^2 T(s) \right) \tag{4.11}$$

which depends on the choice of model for $T(t)$. Equation (4.10) with (4.11) now provides an analytical solution for the function $U(t)$, the unknown untreated incidence of opiate use from the back calculation model of (2.1).

4.2.1 Exponential Growth in First Treatment Contacts.

Firstly the solution to equation (4.10) is considered given the exponential growth in the number of treated opiate cases described by,

$$T(t) = a_0 \, exp(a_1 t). \tag{4.12}$$

$F(s)$ from equation (4.10) and the simple exponential form in equation (4.12) are combined to obtain,

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$$F(s) = C \exp(\lambda s)\Big((a_0 a_1^2 + 2\lambda a_0 a_1 + \lambda^2 a_0) \exp(a_1 s)\Big). \tag{4.13}$$

From equation (4.13) the coefficients are added and the exponentials are combined to give:

$$F(s) = Cg \exp\big((\lambda + a_1)s\big), \tag{4.14}$$

where

$$g = \big(a_0 a_1^2 + 2\lambda a_0 a_1 + \lambda^2 a_0\big). \tag{4.15}$$

The required solution of (4.10), for $U(t)$ when $T(t)$ is an exponential model, is given by,

$$U(t) = Cg \frac{\sin(p\pi)}{\pi} \exp(-\lambda t) \frac{d}{dt} \int_0^t (t-s)^{p-1} \exp\big((\lambda + a_1)s\big) \, ds. \tag{4.16}$$

The integral on the right hand side of equation (4.16) needs to be solved, taking this integral gives:

$$I = \int_0^t (t-s)^{p-1} \exp\big((\lambda + a_1)s\big) \, ds, \tag{4.17}$$

where $-1 < p - 1 < 0$. Letting $u = t - s$, when $s = 0$ then $u = t$ and when $s = t$ then $u = 0$ and $-du = ds$ gives:

$$I = \exp\big((\lambda + a_1)t\big) \int_0^t u^{p-1} \exp\big(-(\lambda + a_1)u\big) \, du. \tag{4.18}$$

Letting $v = (\lambda + a_1)u$ gives:

$$I = \frac{\exp\left((\lambda + a_1)t\right)}{(\lambda + a_1)^p} \int_0^{(\lambda+a_1)t} v^{(p-1)} \exp(-v)\, dv. \tag{4.19}$$

Equation (4.19) can be rewritten as,

$$I = \frac{\exp\left((\lambda + a_1)t\right)}{(\lambda + a_1)^p} \left(\int_0^\infty v^{(p-1)} \exp(-v)\, dv - \int_{(\lambda+a_1)t}^\infty v^{(p-1)} \exp(-v)\, dv \right)$$

$$= \frac{\exp\left((\lambda + a_1)t\right)}{(\lambda + a_1)^p} \{\Gamma(p) - \Gamma[p, (\lambda + a_1)t]\}. \tag{4.20}$$

In order to obtain estimates of the hidden incidence of untreated opiate use, using equation (4.10) the derivative of equation (4.20), I with respect to t must be calculated. Leibnitz rule for the derivative of an integral is used to compute the derivative of the complete and incomplete gamma functions, $\Gamma(p)$ and $\Gamma[p, (\lambda + a_1)t]$ respectively, to get:

$$\frac{d}{dt}\{\Gamma(p) - \Gamma[p, (\lambda + a_1)t]\} = (\lambda + a_1)^p t^{p-1} \exp(-(\lambda + a_1)t). \tag{4.21}$$

From equations (4.20) and (4.21) it can now be stated that,

$$\frac{dI}{dt} = \exp[(\lambda + a_1)t]\frac{\Gamma(p)}{(\lambda + a_1)^{p-1}} + t^{p-1} - R, \tag{4.22}$$

where

$$R = \frac{\exp[(\lambda + a_1)t]}{(\lambda + a_1)^{p-1}}\Gamma[p, (\lambda + a_1)t]. \tag{4.23}$$

Taking equations (4.16) and (4.22) to get,

$$U(t) = Cg\frac{\sin(p\pi)}{\pi}\exp(-\lambda t)\left(\exp\left[(\lambda+a_1)t\right]\frac{\Gamma(p)}{(\lambda+a_1)^{p-1}} + t^{p-1}\right) - \hat{R}, \quad (4.24)$$

where

$$\hat{R} = Cg\left(\frac{\sin(p\pi)}{\pi}\exp(-\lambda t)\right)R. \quad (4.25)$$

Equation 4.24 above is integrated to produce estimates of the incidence of untreated opiate use when the growth in treated incidence is described by an exponential model.

4.2.2 Linear Growth in First Treatment Contacts

When the linear model for $T(t)$ described as

$$T(t) = b_0 + b_1 t \quad (4.26)$$

is taken in combination with $U(t)$ as described by equation (4.10) then $F(s)$ is given by:

$$F(s) = C\exp(\lambda s)\left(2\lambda b_1 + \lambda^2(b_0 + b_1 s)\right). \quad (4.27)$$

Taking equations 4.10 and 4.27, and making the change of variables $u = t - s$, to give:

$$I = \exp(\lambda t)\int_0^t u^{p-1}\exp(-\lambda u)\left(2\lambda b_1 + \lambda^2\left(b_0 + b_1(t-u)\right)\right)du. \quad (4.28)$$

Another change of variables is made, letting $v = \lambda u$, I is split into two terms for ease of manipulation to give $I = I_1 + I_2$. The first equation, I_1 is given by:

$$I_1 = \frac{\lambda(2b_1 + \lambda b_0 + \lambda b_1 t)\exp(\lambda t)}{\lambda^p} \int_0^{\lambda t} v^{(p-1)}\exp(-v)\,dv$$

$$= \frac{\lambda(2b_1 + \lambda b_0 + \lambda b_1 t)\exp(\lambda t)}{\lambda^p}\left(\Gamma(p) - \Gamma(p,\lambda t)\right). \tag{4.29}$$

I_1 is differentiated with respect to t to give,

$$\frac{dI_1}{dt} = \frac{\left(3b_1 + \lambda(b_0 + b_1 t)\right)\exp(\lambda t)}{\lambda^{(p-2)}}\left(\Gamma(p) - \Gamma(p,\lambda t)\right) + \lambda\left(2b_1 + \lambda(b_0 + b_1 t)\right)t^{p-1} \tag{4.30}$$

The second term that makes up I in equation (4.28) is I_2 and is given as:

$$I_2 = \frac{-b_1 \exp(\lambda t)}{\lambda^{(p-1)}} \int_0^\lambda v^p \exp(-v)\,dv. \tag{4.31}$$

Equation 4.31 is integrated by parts to reduce the power p of v, which gives:

$$\frac{-b_1 \exp(\lambda t)}{\lambda^{(p-1)}}\left(-(\lambda t)^p \exp(-\lambda t) + p\int_0^{\lambda t} v^{(p-1)}\exp(-v)\,dv\right), \tag{4.32}$$

which is rewritten as

$$I_2 = \lambda b_1 t^p - \frac{b_1 \exp(\lambda t)p}{\lambda^{(p-1)}}\left(\Gamma(p) - \Gamma(p,\lambda t)\right). \tag{4.33}$$

I_2 is differentiated with respect to t to get,

$$\frac{dI_2}{dt} = \frac{-b_1 \exp(\lambda t)p}{\lambda^{(p-2)}}\left(\Gamma(p) - \Gamma(p,\lambda t)\right). \tag{4.34}$$

A solution for $U(t)$ in equation (4.10) is obtained from equations (4.30) and (4.34),

$$U(t) = \frac{C\sin(p\pi)}{\pi}\left(\left(\frac{\lambda b_0 + b_1(3 + \lambda t - p)}{\lambda^{(p-2)}}\right)\Gamma(p)\right.$$

$$\left. + \exp(-\lambda t)\lambda[b_1(2 + \lambda t) + \lambda b_0]t^{(p-1)}\right) + R, \qquad (4.35)$$

where R is given by,

$$R = \frac{C\sin(p\pi)}{\pi}\frac{\left(b_1(p - 3 + \lambda t) + \lambda b_0\right)}{\lambda^{(p-2)}}\left(\Gamma(p, \lambda t)\right). \qquad (4.36)$$

Equation (4.35) can now be integrated to obtain estimates of the hidden, untreated incidence of opiate use when $T(t)$ is described by a linear model.

4.2.3 Quadratic Growth in First Treatment Contacts

Finally consider $U(t)$ in equation (4.10) when $T(t)$ is given by a quadratic equation as described by:

$$T(t) = c_0 + c_1 t^2, \qquad (4.37)$$

then F(s) is given by:

$$F(s) = C\exp(\lambda s)\left(2c_1 + 4\lambda c_1 s + \lambda^2(c_0 + c_1 s^2)\right). \qquad (4.38)$$

Let $c_2 = \lambda^2 c_1$, $c_3 = 4\lambda c_1$ and $c_4 = \lambda^2 c_0 + 2c_1$ to get:

$$U(t) = \frac{C\sin(p\pi)}{\pi}\exp(-\lambda t)\frac{d}{dt}\int_0^t (t - s)^{p-1}\left(\exp(\lambda s)(c_2 s^2 + c_3 s + c_4)\right)ds. \qquad (4.39)$$

A solution is required to the integral on the right hand side of equation (4.39). I is defined as:

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$$I = \int_0^t (t-s)^{p-1} \Big(\exp(\lambda s)(c_2 s^2 + c_3 s + c_4) \Big) \, \mathrm{d}s. \tag{4.40}$$

The same change of variables is made as in equation (4.28) above to get,

$$I = \int_0^t u^{p-1} \exp \big(-\lambda(t-u) \big) \big(c_2(t-u)^2 + c_3(t-u) + c_4 \big) \, \mathrm{d}u. \tag{4.41}$$

Adding the coefficients of equation (4.41) and let $f(t) = c_2 t^2 + c_3 t + c_4$ to get:

$$I = \exp(\lambda t) \int_0^t u^{p-1} \exp \big(-\lambda u \big) \big(c_2 u^2 - (2c_2 t + c_3)u + f(t) \big) \, \mathrm{d}u. \tag{4.42}$$

I is split into three integrals, $I = I_1 + I_2 + I_3$, with

$$I_1 = c_2 \exp(\lambda t) \int_0^t u^{p+1} \exp(-\lambda u) \, \mathrm{d}u, \tag{4.43}$$

$$I_2 = -(2c_2 t + c_3) \exp(\lambda t) \int_0^t u^p \exp(-\lambda u) \, \mathrm{d}u, \tag{4.44}$$

$$I_3 = \exp(\lambda t) f(t) \int_0^t u^{p-1} \exp(-\lambda u) \, \mathrm{d}u. \tag{4.45}$$

Firstly taking equation (4.43), a change of variables is made by letting $v = \lambda u$ to get,

$$I_1 = \frac{c_2 \exp(\lambda t)}{\lambda^{(p+2)}} \int_0^{\lambda t} v^{(p+1)} \exp(-v) \, \mathrm{d}v. \tag{4.46}$$

Equation (4.46) is integrated by parts, to give

$$I_1 = \frac{c_2 \exp(\lambda t)}{\lambda^{(p+2)}} \left(-(\lambda t)^{p+1} \exp(-\lambda t) + (p+1) \int_0^{\lambda t} v^p \exp(-v) \, \mathrm{d}v \right). \tag{4.47}$$

In order to reduce the power of v, equation (4.47) is integrated by parts to give:

$$I_1 = \frac{-c_2 t^{p-1}}{\lambda} - \frac{c_2(p+1)t^p}{\lambda^2} + \frac{p(p+1)c_2 \exp(\lambda t)}{\lambda^{p+2}} \int_0^{\lambda t} v^{p-1} \exp(-v)\, dv, \qquad (4.48)$$

which is rewritten as,

$$I_1 = \frac{-c_2 t^{p-1}}{\lambda} - \frac{c_2(p+1)t^p}{\lambda^2} + \frac{p(p+1)c_2 \exp(\lambda t)}{\lambda^{p+2}} \left(\Gamma(p) - \Gamma(p, \lambda t) \right). \qquad (4.49)$$

I_1 is differentiated with respect to t and rearranged to give:

$$\frac{dI_1}{dt} = \frac{-(p+1)c_2 t^p}{\lambda} + \frac{p(p+1)c_2 \exp(\lambda t)\Gamma(p)}{\lambda^{p+1}} - R_1, \qquad (4.50)$$

where

$$R_1 = \frac{p(p+1)c_2 \exp(\lambda t)\Gamma(p, \lambda t)}{\lambda^{p+1}}. \qquad (4.51)$$

Take I_2 as in equation (4.44) and make the change of variables, $v = \lambda u$, to get:

$$I_2 = \frac{-(2c_2 t + c_3)\exp(\lambda t)}{\lambda^{p+1}} \int_0^{\lambda t} v^p \exp(-v)\, dv. \qquad (4.52)$$

Equation (4.52) is integrated by parts to give,

$$I_2 = \frac{-(2c_2 t + c_3)\exp(\lambda t)}{\lambda^{p+1}} \left(-(\lambda t)^p \exp(-\lambda t) + p \int_0^{\lambda t} v^{p-1} \exp(-v)\, dv \right), \qquad (4.53)$$

which is rewritten as

$$I_2 = \frac{-(2c_2 t + c_3)t^p}{\lambda} - \frac{p(2c_2 t + c_3)\exp(\lambda t)}{\lambda^{p+1}} \left(\Gamma(p) - \Gamma(p, \lambda t) \right). \qquad (4.54)$$

In order to estimate $U(t)$ in equation (4.10), it is necessary to find $\frac{dI_2}{dt}$, which is obtained by differentiating equation (4.54) to give:

$$\frac{dI_2}{dt} = \frac{2c_2 t^p}{\lambda} - \left(\frac{2c_2}{\lambda^{(p+1)}} + \frac{(2c_2 t + c_3)}{\lambda^p} \right) p \exp(\lambda t) \Gamma(p) + R_2, \qquad (4.55)$$

where

$$R_2 = \left(\frac{2c_2}{\lambda^{(p+1)}} + \frac{(2c_2 t + c_3)}{\lambda^p} \right) p \exp(\lambda t) \Gamma(p, \lambda t). \qquad (4.56)$$

Finally take I_3 in equation (4.45) and make the change of variables $v = \lambda u$ to get,

$$I_3 = \frac{\exp(\lambda t) f(t)}{\lambda^p} \int_0^{\lambda t} v^{(p-1)} \exp(-\lambda t) \, dv, \qquad (4.57)$$

which is rewritten as,

$$I_3 = \frac{\exp(\lambda t) f(t)}{\lambda^p} \left(\Gamma(p) - \Gamma(p, \lambda t) \right). \qquad (4.58)$$

To find $\frac{dI_3}{dt}$, equation (4.58) is differentiated to give,

$$\frac{dI_3}{dt} = \Gamma(p) \left(\frac{\exp(\lambda t) f(t)}{\lambda^{p-1}} + \frac{\exp(\lambda t) f'(t)}{\lambda^p} + f(t) t^{p-1} \right) - R_3, \qquad (4.59)$$

where

$$R_3 = \Gamma(p, \lambda t) \left(\frac{\exp(\lambda t) f(t)}{\lambda^{p-1}} + \frac{\exp(\lambda t) f'(t)}{\lambda^p} \right). \qquad (4.60)$$

Equations (4.50), (4.55) and (4.59) are added to give:

$$\frac{dI}{dt} = \Gamma(p)\exp(\lambda t)\left(\frac{f(t)}{\lambda^{p-1}} + \frac{f'(t)}{\lambda^p} - p\left(\frac{c_2(1-p)}{\lambda^{p+1}} + \frac{2c_2 t + c_3}{\lambda^p}\right)\right)$$

$$+ \frac{(1-p)c_2 t^p}{\lambda} + f(t)t^{p-1} - R, \tag{4.61}$$

where

$$R = -R_1 + R_2 - R_3$$

$$= \Gamma(p, \lambda t)\exp(\lambda t)\left(\frac{f(t)}{\lambda^{p-1}} + \frac{f'(t)}{\lambda^p} - p\left(\frac{c_2(1-p)}{\lambda^{p+1}} + \frac{2c_2 t + c_3}{\lambda^p} + \frac{p^2 c_2}{\lambda^{p+1}}\right)\right) \tag{4.62}$$

From equations (4.10), (4.38) and (4.62) a solution for $U(t)$ is given by:

$$U(t) = \frac{C\sin(p\pi)}{\pi}\left(\left(\frac{f(t)}{\lambda^{p-1}} + \frac{f'(t)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 t + c_3}{\lambda^p}\right) + \frac{p^2 c_2}{\lambda^{p+1}}\right)\Gamma(p)\right.$$

$$\left. + \left(\frac{c_2 t^p(1-p)}{\lambda} + f(t)t^{p-1}\right)\exp(-\lambda t)\right) - \hat{R}, \tag{4.63}$$

where $\hat{R}$ is given by,

$$\hat{R} = \frac{C\sin(p\pi)}{\pi}\left(\frac{f(t)}{\lambda^{p-1}} + \frac{f'(t)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 t + c_3}{\lambda^p}\right) + \frac{p^2 c_2}{\lambda^{p+1}}\right)\Gamma(p, \lambda t). \tag{4.64}$$

The analytical solutions derived for $U(t)$ are now applied to the problem of estimating the incidence of untreated opiate use in Ireland.

4.3 Results - The Hidden, Untreated Incidence of Opiate Use, U(t)

For each of the three models of $T(t)$, the number of first treatment cases for opiate use in year t, the parameters are as given in chapter 2. The model for the rate of progression to treatment, $f(t)$ is given by the Gamma distribution $\Gamma(\alpha, \lambda)$, with $\alpha = 2.46$ and $\lambda = 0.57$ as given in chapter 3. Once again the expected annual incidence of untreated opiate use can be estimated by integrating the rate of untreated opiate use, $U(t)$ using,

$$U_i = \int_{i-1998}^{i-1997} U(t)\,\mathrm{d}t. \tag{4.65}$$

The expected annual incidence of hidden, untreated opiate use, U_i is estimated assuming the three forms of $T(t)$ in equations (4.12), (4.26) and (4.37) and $f(t)$ modelled by a Gamma distribution.

For $T(t)$ given by an exponential model, $U(t)$ is given by equation (4.24) with parameters given in Table 4.1 below.

Parameter	Value
C	7.674
g	282.039
$\Gamma(2.46)$	1.293
$\Gamma(0.57)$	1.562
$\frac{\sin(p\pi)}{\pi}$	0.316

Table 4.1: Parameter estimates of $U(t)$ in equation (4.24), (4.35), (4.63)

These parameters combined with equation (2.27) and the parameters given in chapter 2 for a_0 and a_1 give rise to the estimates of untreated incidence of opiate use presented in Table 4.2.

Year	Without Error Bound	With Error Bound
1999	1140 [837, 1520]	723 [510, 1004]
2000	959 [700, 1287]	755 [534, 1042]
2001	729 [531, 980]	642 [458, 880]
2002	519 [378, 699]	485 [348, 661]
2003	355 [258, 478]	342 [246, 464]
2004	235 [171, 318]	231 [167, 312]
2005	153 [111, 206]	151 [109, 204]
Total	4089 [2986, 5488]	3330 [2372, 4568]

Table 4.2: Expected annual incidence of hidden, untreated opiate use with 95% confidence interval, $T(t)$ exponential equation (4.12).

Incidence estimates of hidden, untreated opiate use in Ireland from 1999 to 2005, when $T(t)$ is given by a linear model with the parameters b_0 and b_1 as estimated in chapter 3 and the parameters in Table 4.1 are presented in Table 4.3.

Year	Without Error Bound	With Error Bound
1999	402 [262, 539]	222 [137, 307]
2000	175 [105, 245]	92 [51, 134]
2001	82 [44, 119]	42 [21, 64]
2002	40 [19, 60]	20 [8, 32]
2003	19 [8, 31]	10 [3, 16]
2004	10 [3, 16]	5 [1, 8]
2005	5 [1, 8]	2[0, 4]
Total	733 [442, 1018]	393 [221, 565]

Table 4.3: Expected annual incidence of hidden, untreated opiate use with 95% confidence interval, $T(t)$ linear equation (4.26).

Finally the parameters from Table 4.1 are once again combined with equation (2.27) and the parameters given in chapter 2 for c_0 and c_1 gives rise to the to the estimates of untreated incidence of opiate use in Ireland from 1999 to 2005 as presented in Table 4.4.

Year	Without Error Bound	With Error Bound
1999	1080 [873, 1288]	889 [709, 1070]
2000	876 [647, 1105]	790 [578, 1002]
2001	752 [485, 1018]	712 [457, 967]
2002	651 [337, 965]	632 [326, 939]
2003	554 [184, 924]	546 [181, 911]
2004	455 [21, 888]	451 [20, 882]
2005	349 [-155, 853]	347 [-155, 850]
Total	4717 [2392, 7042]	4368 [2116, 6621]

Table 4.4: Expected annual incidence of hidden, untreated opiate use with 95% confidence interval, $T(t)$ quadratic equation (4.37).

4.4 Conclusions and Discussion

The back calculation model has been explicitly solved assuming a range of forms for the change in treated incidence of drug use combined with the Gamma distribution to model the rate of progression to treatment. These solutions have been applied to the problem of estimating the incidence of hidden untreated opiate use in Ireland from 1999 to 2005. Tables 4.2, 4.3 and 4.4 illustrate a pattern of decreasing incidence of hidden untreated opiate use in Ireland from 1999 to 2005. It can be seen from Tables 4.2, 4.3 and 4.4 that the point estimates of total incidence of untreated opiate use in Ireland range from 733 to 4,717. The incidence estimates produced in this chapter are not an improvement on the estimates in chapter 2 despite the fact that

the exact rate of progression to treatment is known and used in the model. This reinforces the finding in chapter 2 that the predicted incidence does not in fact depend more on the choice of the incubation period distribution than on the choice of model for treated incidence in the opiate use application which deviates from the findings of Comiskey & Ruskin (1992) in their application to HIV incidence.

Once again it must be noted that it is not strictly possible to validate the incidence estimates produced as no previous incidence estimates have been published to date. However in chapter 3 the lack of international data on the rate of progression to treatment documented by Rossi (1999) was addressed and the exact rates of progression to treatment modelled were used in presenting a new solution to the back calculation equation.

In spite of the limitations highlighted in the methodology and the width of the prediction intervals the method and solutions presented contribute significantly to bridging the gap in knowledge by providing the first estimates of hidden incidence of opiate use in Ireland. The models and solutions presented provide European researchers with a means of producing first incidence estimates among their countries based on the Pompidou protocol treatment demand indicator.

Whilst it is possible to produce cost effective estimates of incidence using the model outlined, it is essential that the aim of Department of Community, Rural and Gaeltacht Affairs (2009), to ensure the availability of accurate and timely data on the problem of substance misuse in Ireland is met in order to produce current and regular estimates. The back calculation technique could also be used to project the future incidence of untreated opiate use should the Department of Community, Rural and Gaeltacht Affairs (2009) achieve their goal in relation to data availability.

4.5   Chapter Summary

In this chapter models were derived for the untreated incidence opiate use, $U(t)$. The models were then integrated to produce estimates of the hidden, untreated incidence of use in Ireland from 1999 to 2005. In the next chapter the range of forms derived for $U(t)$, the untreated incidence along with the three forms of $T(t)$, the treated incidence will be used to estimate the prevalence of opiate use in Ireland.

Chapter 5

Estimating the Prevalence of Opiate Use in Ireland

5.1 Introduction

Across the world, international organisations have discussed the need for continued research into the extent and spread of illegal drug use. The European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) produces annual reports and trends on treated drug use across Europe and has invested considerable time and money into producing guidelines for researchers on estimating the prevalence of hidden drug use, most notably hidden opiate use (EMCDDA 1999). Indeed according to the United Nations Office on Drugs and Crime (2004), in terms of health impact, opiates are the world's most serious problem drug. Research into the prevalence of opiate use across various cities and countries of Europe has been conducted at considerable expense. In Ireland, total government expenditure on the drug problem was approximately €390 million in 2005 rising to over €422 million in 2006 (Alcohol and Drug Research Unit of the Health Research Board 2008a). Within the new emerging nations of Europe estimates of prevalence of problem drug use are less widely available. The EMCDDA has contributed greatly to the need to provide health and social policy makers and researchers with prevalence estimation methods.

However more research is required on prevalence estimation techniques that can be applied regularly and that can be adapted to suit emerging drug trends.

Previous chapters have developed models, based on mathematical models from AIDS epidemiology to produce estimates of the incidence of untreated opiate use. This chapter introduces a basic model for estimating the prevalence of opiate use. It describes the model and the different forms the model takes based on the incidence models derived in chapters 2 and 4. The specific aims of this chapter are:

- To develop a new approach to estimate the prevalence of problem opiate use using first treatment data and untreated incidence data.

- To implement the model developed to produce estimates of the prevalence of opiate use in Ireland.

- To establish if the rate of progression to treatment for opiate use affects the estimates produced.

5.1.1 Methods for Estimating the Prevalence of Illegal Drug Use

Previous estimates of the prevalence of problem drug use, particularly the prevalence of opiate or heroin use have been obtained using different methods such as the capture-recapture method (EMCDDA 1997b, Comiskey 2001, Choi & Comiskey 2003, Comiskey & Barry 2001, Kelly *et al.* 2003, 2009), the multi-source enumeration method (EMCDDA 1997a,b), the multiplier method (Hartnoll *et al.* 1985), the truncated poisson method (Choi & Comiskey 2003) and more technically advanced models have been proposed by (De Angelis *et al.* 2004). De Angelis *et al.* (2004) utilised the back calculation method with data on drug deaths to provide estimates

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of prevalence of opiate use. Some of the different techniques used to estimate the prevalence of drug use are discussed in the next section.

The Capture-recapture Method

The capture-recapture method originated in ecology (Spoor *et al.* 1996) and has since been used in many different applications to estimate prevalence. The method involves capturing an initial sample of the population to be measured, tagging the individuals caught and releasing the sample. A second sample is then taken, the sample is measured and the number of recaptured, i.e. previously tagged individuals is recorded. The principle behind the method is the proportion marked in the second sample equals the proportion marked in the whole population. The mathematical model for the capture-recapture method is expressed as:

$$\frac{a}{d} = \frac{c}{b}$$

where the initial sampled captured is denoted by a, the second sample captured is given by b, the number recaptured is defined as c and d denotes the wholes population.

An advantage of the method is it is relatively straightforward to apply to available data, however the accuracy of the model depends on certain assumptions, which if violated cast doubt on its use in epidemiology (Comiskey 2001). For example, Comiskey's three source model for estimating the prevalence of opiate use in Ireland assumes that there is no dependence between the three data sources. This independence assumption is necessary for all capture-recapture studies. It is also assumed that each individual is equally likely to be captured and there is no change in the

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study population (Choi & Comiskey 2003), that is the population is closed with no movement in or out. A disadvantage of this method is that, if one or both of these assumptions are violated, it is possible that under or over estimates of prevalence can be obtained.

The Multi-source Enumeration Method

The case-finding method was originally used as a first description of death and disease in a population, however it is not a suitable method on its own to produce estimates of prevalence as there is no single information source that paints a full picture of the drug using population (EMCDDA 1997a). However, case finding is the basis of many estimation techniques such as the multi-source enumeration or intensive case-finding technique. This method takes a combination of information sources such as treatment registers and police data to produce prevalence estimates. The multi-source enumeration method as used by Comiskey (2001) is plausible for a small population, such a small town. However to avoid double-counting it is necessary to identify overlaps and this can lead to disclosure of confidential client information which is unethical. Disadvantages of the case-finding method are the cost and time required to gather the necessary data and follow up the cohort involved. As a result of these disadvantages the method is not feasible for large populations.

The Multiplier Method

Law *et al.* (2006) describes the multiplier method as one of the simplest methods to adopt to produce prevalence estimates and discusses how the method can be applied to recent data. In order to estimate the size of the total drug using population, the method requires knowledge of a benchmark, and a multiplier. The benchmark is

the number of identified problem drug users, for example the number of arrests for drug use. The multiplier is the probability of someone of the unknown population being in the sample, for example the related multiplier is taken as the proportion from some sample survey that were arrested for drug use that year. The unknown population size, can then be estimated by:

$$d = \frac{b}{m}$$

where b is the benchmark, m is the multiplier and d is the unknown population to be estimated.

The death multiplier has been used by Hartnoll *et al.* (1985) and Comiskey (2001) to estimate the prevalence of illicit drug use. Comiskey (2001) used the death multiplier method to estimate the prevalence of opiate use in Ireland. In order to produce accurate prevalence estimates the mortality rate must be correct and constant and therefore depends on accurate record keeping. Law *et al.* (2006) discusses the different mortality rates associated with the method of drug consumption, i.e. those who choose to inject have a different mortality rate to those who sniff or smoke opiates. Clearly, while the mortality multiplier method is technically easy to compute, it is dependent on knowing the appropriate death rate to apply. This in turn can differ with region, gender, the nature of the drug use (snort, inject, etc.) and the combination of drugs used (opiates, cocaine, benzodiazepines, cannabis, alcohol, and polydrug use). Whilst knowing the appropriate death rate to apply is vital to this method a limitation of the death multiplier method is that data on opiate related deaths may not be readily available.

Multiple Indicator Method

The multiple indicator method is another popular prevalence estimation method. The method combines available prevalence information for a few regions, the size of the risk population and indicators of drug use that are available for all areas (Frisher *et al.* 2001). This method requires reliable prevalence estimates for at least two other regions, these regions are known as anchor points. The method assumes a linear relationship between prevalence and regions if only two regions are used. In addition, estimates for these two other regions are usually obtained using another method such as the capture-recapture method. Some examples of indicators as described by Frisher *et al.* (2001) and Comiskey (2001) which could be chosen for prevalence estimates of illegal drug use are:

- Convictions for drug related offences.

- Drug related deaths.

- Drug treatment cases.

- Injecting drug use related AIDS cases.

- Seizures of controlled drugs.

Principal component analysis is then carried out to extract the main factor which explains the largest amount of variance in the indicators (Frisher *et al.* 2001). The method assumes that there is a relationship between the unobserved prevalence and the observed indicators and the observed indicators of the anchor points are applicable to other geographical regions. A disadvantage of the multiple indicator method is that it is not only bound by the limitations and assumptions of its own

methodology but also by the limitations and assumptions of the methodology used to produce estimates for the other two anchor point regions.

Researchers have been able to achieve reasonable estimates of prevalence using all of these methods, however these methods are not necessarily the easiest to implement nor are they the most cost effective or efficient methods of obtaining prevalence estimates. Therefore a new approach for estimating the prevalence of problematic opiate use that is not heavily data dependent and can be used to predict prevalence given a range of scenarios or changes in the growth patterns of first treatment contacts and incidence would be beneficial to researchers, policy-makers and service providers.

5.2 Methodology

The model selected to estimate the prevalence of opiate use is based on mathematical models from AIDS epidemiology. The model was chosen for the following reasons:

- It is not heavily data dependent so it is cost effective to apply.

- It is not limited to estimating the prevalence of the use of a particular drug for example it can be applied to the problem of estimating the prevalence of all drug use.

- It is not restricted to use with national data, it can be applied to international data thus the model is applicable globally.

Integral equations have been used in the past to estimate the prevalence of AIDS (Department of Health and Social Security 1988, Comiskey 1991). The number of AIDS cases was the difference between the number of diagnosed AIDS cases and the

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number of deaths therefore the prevalence $p(t)$ was defined as the number of live AIDS cases at time t. This was expressed by,

$$p(t) = \int_0^t \big(a(u) - d(u)\big)\,\mathrm{d}u \tag{5.1}$$

where the prevalence in year t is given by the sum of the incidence of AIDS cases, $a(u)$ less those leaving the AIDS class through death, $d(u)$, as the objective of Department of Health and Social Security (1988) and Comiskey (1991) was to estimate the number of live AIDS cases, $p(t)$.

A similar approach is considered in a bid to estimate the prevalence of opiate use in Ireland. The prevalence of opiate use at time t is denoted by $P(t)$ and is given by the integral equation,

$$P(t) = \int_0^t U(u) + T(u) - \big(\delta(U(u))\big)\,\mathrm{d}u \tag{5.2}$$

where $U(u)$ is the hidden or untreated incidence of opiate use at time u, $T(u)$ is the number of first treatments for opiate use at time u and $\delta(U(u))$ is the proportion of the untreated incidence which progresses to first treatment at time u. The assumptions of this model are,

- The number of first treatment contacts for opiate use are known.

- An opiate user will progress to first treatment after an average incubation time, $\frac{1}{\mu}$.

- The number of deaths is very small.

In summary prevalence is defined here as the sum of the incidence of hidden, untreated opiate use, $U(u)$, plus the sum of the incidence of first treatment contacts

$T(u)$ less the proportion of untreated incidence that progress to first treatment, $\delta(U(u))$. In equation (5.1) both Department of Health and Social Security (1988) and Comiskey (1991) subtract those leaving the AIDS class through death, $d(u)$, as it is no longer necessary to count these individuals as prevalence is defined as the number of live AIDS cases. However for the purpose of this research the estimate required is the prevalence of all living opiate users therefore the untreated and treated incidence of opiate use are summed. In order to avoid double counting, the element $\delta(U(u))$, is included in the prevalence model expressed in equation (5.2) as it is known that an untreated opiate user will progress to first treatment after an average period of time using opiates. The average rate of progression to first treatment for an opiate user can be defined as μ therefore the yearly proportion of untreated opiate users that progress to first treatment can be expressed as $\delta = \frac{1}{\mu}$. Prevalence was defined in chapter 2 as the total number of cases of untreated opiate use in a given population at a specified time (Last 2001). Prevalence estimates are obtained from equation (5.2) as it sums the number of hidden opiate users and the number of untreated opiate users less the number of untreated opiate users entering treatment at a specified time hence giving all cases of untreated opiate use.

The type of equation or form for $T(u)$ is based on the known growth in the number of first treatment contacts for the drug used, in this case opiates. The rates of first treatment contacts, $T(u)$, is given by one of the three forms chosen in chapter 2.

Case 1. The number of individuals who present for their first problematic opiate treatment at time u is assumed to be either increasing or decreasing exponentially with u. Hence $T(u)$ is given by,

$$T(u) = a_0 \exp(a_1 u). \tag{5.3}$$

Case 2. The number of individuals who present for their first treatment for opiate use at time u is assumed to be either increasing or decreasing linearly with u. Hence $T(u)$ is given by,

$$T(u) = b_0 + b_1 u. \tag{5.4}$$

Case 3. Finally if the number first treatment contacts for opiate use at time u is assumed to be either expanding or decaying quadratically then $T(u)$ is given by,

$$T(u) = c_0 + c_1 u^2. \tag{5.5}$$

In Chapters 2 and 4 different models based on knowledge of progression to treatment were derived for $U(u)$ the hidden, untreated incidence of opiate use . Accordingly these new models derived for the prevalence of problematic opiate use, $P(t)$, account for when the exact rate of progression to first treatment is unknown as in Chapter 2 and also when the exact rate of progression to treatment is known as in Chapter 4.

In chapter 2 analytical solutions were developed for $U(u)$ as the exact rate of progression to treatment was unknown. The incidence of untreated opiate use, $U(u)$ was derived from the known rates $T(u)$ in equations (5.3), (5.4) and (5.5) when $f(u)$ the rate of progression to first treatment followed a Gamma distribution with $\alpha \in N$. When the exact rate of progression to treatment is unknown and so is described by a Gamma distribution with $\alpha = 1$, then $U(u)$ can be expressed by the following

equation:

$$U(u) = \frac{1}{\lambda}\frac{dT}{du} + T(u). \tag{5.6}$$

When the exact rate of progression to treatment is unknown a Gamma distribution with $\alpha = 2$ is considered resulting in $U(u)$ of the form:

$$U(u) = \frac{1}{\lambda^2}\frac{d^2T}{du^2} + \frac{2}{\lambda}\frac{dT}{du} + T(u). \tag{5.7}$$

Equations (5.6) and (5.7) depend on the choice of model for $T(u)$, which was outlined in equations (5.3), (5.4) and (5.5) above. It can be seen from equations (5.6) and (5.7) that the order of $U(u)$ is given by the value of α when $\alpha \in \mathbb{N}$, and the coefficients of $U(u)$ are binomial in form therefore it is possible to estimate prevalence to for any $\alpha \in \mathbb{N}$ when the model for $T(u)$ is known. For example if $\alpha = 3$ then $P(t)$ is given by,

$$P(t) = \int_0^t \frac{1}{\lambda^3}\frac{d^3T}{du^3} + \frac{3}{\lambda^2}\frac{d^2T}{du^2} + \frac{3}{\lambda}\frac{dT}{du} + T(u) - \delta\left(\frac{1}{\lambda^3}\frac{d^3T}{du^3} + \frac{3}{\lambda^2}\frac{d^2T}{du^2} + \frac{3}{\lambda}\frac{dT}{du}\right) du. \tag{5.8}$$

From equation (5.8) it can be seen that the prevalence of problematic opiate use can be easily estimated without actually having to estimate incidence of hidden drug use, once the rate of progression to treatment is known to follow a Gamma distribution denoted $\Gamma(\alpha, \lambda)$, as long as α is a positive integer, as the order of $P(t)$ is given by the value of α and the coefficents are binomial in form.

Following work on modelling the latency period of opiate use in chapter 3 solutions were developed for $U(u)$ in chapter 4, as the exact rate of progression to treatment was known. The incidence of untreated opiate use, $U(u)$ was derived

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from the known rates $T(u)$ in equations (5.3), (5.4) and (5.5) when $f(u)$ the rate of progression to first treatment followed a Gamma distribution with $\alpha \in \mathbb{R}$.

The mathematical model in equation (5.2), used to estimate prevalence is based on first treatment and untreated incidence of problematic opiate use. In order to estimate the prevalence of problematic opiate use knowledge of $T(u)$ and $U(u)$ are used to setup the prevalence model. There are five forms considered for $P(t)$, when the exact rate of progression to treatment is unknown, and three forms considered for $P(t)$ when the exact rate of progression to treatment is known. These forms of $P(t)$ depend on the different forms of $T(u)$ from equations (5.3), (5.4) and (5.5)

5.2.1 Case 1. Exponential model of T(u)

Firstly when the exponential form of $T(u)$ in equation (5.3) is considered and $U(u)$ is modelled using equation (5.6), then $P(t)$ is given by,

$$P_1(t) = \int_0^t \frac{a_0 a_1 \exp(a_1 u)}{\lambda} + 2a_0 \exp(a_1 u) - \delta\left(\frac{a_0 a_1 \exp(a_1 u)}{\lambda} + a_0 \exp(a_1 u)\right) du$$

$$= \int_0^t a_0 \exp(a_1 u)\left(\frac{a_1}{\lambda} + 2 - \frac{\delta a_1}{\lambda} - \delta\right) du. \tag{5.9}$$

Next a model is considered for $P(t)$ when the rate of progression to treatment is assumed to follow a Gamma distribution with the parameter $\alpha = 2$. The exponential model for $T(u)$ in equation (5.3) in combination with $U(u)$ in equation (5.7) lead to the following model of $P(t)$,

$$P_2(t) = \int_0^t \frac{a_0 a_1 \exp(a_1 u)}{\lambda^2} + \frac{2 a_0 a_1 \exp(a_1 u)}{\lambda} + 2 a_0 \exp(a_1 u)$$

$$-\delta \left(\frac{a_0 a_1 \exp(a_1 u)}{\lambda^2} + \frac{2 a_0 a_1 \exp(a_1 u)}{\lambda} + a_0 \exp(a_1 u) \right) du$$

$$= \int_0^t a_0 \exp(a_1 u) \left(\frac{a_1}{\lambda} \left(\frac{1}{\lambda} + 2 - \frac{\delta}{\lambda} - 2\delta \right) + 2 - \delta \right) du. \qquad (5.10)$$

Finally the exponential form of $T(u)$ in equation (5.3) is considered when the exact latency period is known and the corresponding form derived for $U(u)$ is given by:

$$U(u) = Cg \frac{\sin(p\pi)}{\pi} \exp(-\lambda u) \left(\exp\left[(\lambda + a_1)u\right] \frac{\Gamma(p)}{(\lambda + a_1)^{p-1}} + u^{p-1} - R \right), \qquad (5.11)$$

where R is given by,

$$R = \frac{\exp\left((\lambda + a_1)u\right)}{(\lambda + a_1)^{p-1}} \Gamma[p, (\lambda + a_1)u]. \qquad (5.12)$$

The resulting equation for $P(t)$, when equation (5.6) and (5.11) are substituted into equation (5.2) is expressed as:

$$P_3(t) = \int_0^t C g \frac{\sin(p\pi)}{\pi} \exp(-\lambda u) \left(\exp\left[(\lambda + a_1)u\right] \frac{\Gamma(p)}{(\lambda + a_1)^{p-1}} + u^{p-1} - R \right) + a_0$$

$$\exp(a_1 u) - \delta \left(C g \frac{\sin(p\pi)}{\pi} \exp(-\lambda u) \left(\exp\left[(\lambda + a_1)u\right] \frac{\Gamma(p)}{(\lambda + a_1)^{p-1}} + u^{p-1} - R \right) \right) du,$$

$$(5.13)$$

which can be rearranged to give:

$$P_3(t) = \int_0^t (1-\delta)C \, g \frac{\sin(p\pi)}{\pi} \exp(-\lambda u) \left(\exp\left[(\lambda+a_1)u\right] \frac{\Gamma(p)}{(\lambda+a_1)^{p-1}} + u^{p-1} - R \right)$$

$$+a_0 \exp(a_1 u) \, du. \tag{5.14}$$

5.2.2 Case 2. Linear model of T(u)

The model for $P(t)$, when the linear form of $T(u)$ in equation (5.4) in combination with $U(u)$ in equation (5.6) when $\alpha = 1$ are substituted into equation (5.2) is given by:

$$P_4(t) = \int_0^t \frac{b_1}{\lambda} + 2b_0 + 2b_1 u - \delta\left(\frac{b_1}{\lambda} + b_0 + b_1 u\right) du$$

$$= \int_0^t b_1\left(\frac{1}{\lambda} + 2u - \frac{\delta}{\lambda} + u\right) + b_0(2-\delta) \, du. \tag{5.15}$$

When $T(u)$ is described by equation (5.4) the resulting form of $U(u)$, as developed in chapter 4 is given by,

$$U(u) = \frac{C \sin(p\pi)}{\pi} \left(\left(\frac{\lambda b_0 + b_1(3 + \lambda u - p)}{\lambda^{(p-2)}} \right) \Gamma(p) \right.$$

$$\left. + \exp(-\lambda t)\lambda\left(b_1(2+\lambda u) + \lambda b_0\right)u^{(p-1)} + R \right), \tag{5.16}$$

where R is given by,

$$R = \frac{\left(b_1(p-3+\lambda u) + \lambda b_0\right)}{\lambda^{(p-2)}} \left(\Gamma(p,\lambda u)\right). \tag{5.17}$$

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Equations (5.4) and (5.16) are substituted into equation (5.2) to derive the following equation for $P(t)$:

$$P_5(t) = \int_0^t \frac{C\sin(p\pi)}{\pi} \left(\left(\frac{\lambda b_0 + b_1(3 + \lambda u - p)}{\lambda^{(p-2)}} \right) \Gamma(p) \right.$$

$$\left. + \exp(-\lambda t)\lambda \left(b_1(2 + \lambda u) + \lambda b_0 \right) u^{(p-1)} + R \right)$$

$$+ b_0 + b_1 u - \delta \left(\frac{C\sin(p\pi)}{\pi} \left(\left(\frac{\lambda b_0 + b_1(3 + \lambda u - p)}{\lambda^{(p-2)}} \right) \Gamma(p) \right. \right.$$

$$\left. \left. + \exp(-\lambda t)\lambda \left(b_1(2 + \lambda u) + \lambda b_0 \right) u^{(p-1)} + R \right) \right) du \qquad (5.18)$$

which can be rewritten as,

$$P_5(t) = \int_0^t (1 - \delta) \frac{C\sin(p\pi)}{\pi} \left(\left(\frac{\lambda b_0 + b_1(3 + \lambda u - p)}{\lambda^{(p-2)}} \right) \Gamma(p) \right.$$

$$\left. + \exp(-\lambda t)\lambda \left(b_1(2 + \lambda u) + \lambda b_0 \right) u^{(p-1)} + R \right) + b_0 + b_1 u \, du. \qquad (5.19)$$

5.2.3   Case 3. Quadratic form of T(u)

When the quadratic form of $T(u)$ in equation (5.5) in combination with $U(u)$ in equation (5.6), is considered then $P(t)$ is given by,

$$P_6(t) = \int_0^t \frac{2c_1 u}{\lambda} + 2c_0 + 2c_1 u^2 - \delta\left(\frac{2c_1 u}{\lambda} + c_0 + c_1 u^2\right) du$$

$$= \int_0^t c_1 u\left(\frac{2}{\lambda} + 2u - \delta\left(\frac{2}{\lambda} + u\right)\right) + c_0(2 - \delta) du. \qquad (5.20)$$

A model is then considered for $P(t)$ when the rate of progression to treatment is assumed to follow a Gamma distribution with the parameter $\alpha = 2$. The quadratic model for $T(u)$ in equation (5.5) in combination with $U(u)$ in equation (5.7) leads to the following model of $P(t)$,

$$P_7(t) = \int_0^t \frac{2c_1}{\lambda^2} + \frac{4c_1}{\lambda} + 2c_0 + 2c_1 u^2 - \delta\left(\frac{2c_1}{\lambda} + \frac{4c_1 u}{\lambda} + 2c_0 + c_1 u^2\right) du \qquad (5.21)$$

Finally when $T(u)$ is given by equation (5.5) the associated form of $U(u)$ derived in chapter 4 is described by,

$$U(u) = \frac{C \sin(p\pi)}{\pi}\left(\left(\frac{f(u)}{\lambda^{p-1}} + \frac{f'(u)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 u + c_3}{\lambda^p}\right) + \frac{p^2 c_2}{\lambda^{p+1}}\right)\Gamma(p)\right.$$

$$\left. + \left(\frac{c_2 u^p(1 - p)}{\lambda} + f(u)u^{p-1}\right)\exp(-\lambda u) - \hat{R}\right), \qquad (5.22)$$

where $\hat{R}$ is given by,

$$\hat{R} = \left(\frac{f(u)}{\lambda^{p-1}} + \frac{f'(u)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 u + c_3}{\lambda^p}\right) + \frac{p^2 c_2}{\lambda^{p+1}}\right)\Gamma(p, \lambda u). \qquad (5.23)$$

$P(t)$, when equation (5.6) and (5.22) are substituted into equation (5.2) is expressed as:

$$P_8(t) = \int_0^t \frac{C \sin(p\pi)}{\pi} \left(\left(\frac{f(u)}{\lambda^{p-1}} + \frac{f'(u)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 u + c_3}{\lambda^p} \right) + \frac{p^2 c_2}{\lambda^{p+1}} \right) \Gamma(p) \right.$$

$$+ \left(\frac{c_2 u^p (1-p)}{\lambda} + f(u)u^{p-1} \right) \exp(-\lambda u) - \hat{R} \right) + c_0 + c_1 u^2$$

$$- \delta \left(\frac{C \sin(p\pi)}{\pi} \left(\left(\frac{f(u)}{\lambda^{p-1}} + \frac{f'(u)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 u + c_3}{\lambda^p} \right) + \frac{p^2 c_2}{\lambda^{p+1}} \right) \Gamma(p) \right.$$

$$+ \left(\frac{c_2 u^p (1-p)}{\lambda} + f(u)u^{p-1} \right) \exp(-\lambda u) - \hat{R} \right) \Bigg) \mathrm{d}u \qquad (5.24)$$

which can be rewritten as,

$$P_8(t) = \int_0^t (1-\delta) \frac{C \sin(p\pi)}{\pi} \left(\left(\frac{f(u)}{\lambda^{p-1}} + \frac{f'(u)}{\lambda^p} - p\left(\frac{c_2}{\lambda^{p+1}} + \frac{2c_2 u + c_3}{\lambda^p} \right) \right. \right.$$

$$+ \frac{p^2 c_2}{\lambda^{p+1}} \right) \Gamma(p) + \left(\frac{c_2 u^p (1-p)}{\lambda} + f(u)u^{p-1} \right) \exp(-\lambda u) - \hat{R} \right) + c_0 + c_1 u^2 \, \mathrm{d}u.$$

$$(5.25)$$

The models $P_1(t)$, $P_2(t)$, $P_3(t)$, $P_4(t)$, $P_5(t)$, $P_6(t)$, $P_7(t)$ and $P_8(t)$ when integrated produce estimates of prevalence of problematic opiate use.

5.3 Results

This method was applied to data on first treatment contacts for all opiates, including heroin in Ireland between 1999 and 2005. Regression analysis, as described in chapter 2 was used to derive the parameters of equations (5.3), (5.4) and (5.5).The resulting equations for $T(u)$ are described in Table 5.1 below.

Type of Growth or Decay in First Treatment Contact	$T(u)$: Rate of First Treatment Contacts in Year u	R^2
Case 1. Exponential Decay	$1015.52 \exp(-0.043u)$	0.71
Case 2. Linear Decay	$1007.86 - 37.07u$	0.72
Case 3. Quadratic Decay	$950.96 - 4.57u^2$	0.73

Table 5.1: Models for the incidence known of first treatment contacts, $T(u)$

In each of the equations for $P(t)$ when the exact rate of progression to treatment is unknown, that is when the rate of progression to treatment is assumed to follow a Gamma distribution with $\alpha = 1$ or $\alpha = 2$, δ is derived from the mean time to first treatment for opiate use of 3.7 years as estimated by Comiskey & Cox (2007). The resulting estimate for δ is 0.27. When the exact rate of progression to treatment is known $\delta = 0.23$. This choice of δ for equation (5.2) is based on the estimated mean incubation period, which is the time from first opiate use to first treatment for opiate use which was estimated in chapter 3, where the mean time to first treatment was observed to be 4.3 years in section 3.4.

5.3.1 Results - Prevalence Estimates

The parameters in Table 5.1 combined with equations (5.9), (5.10), (5.15), (5.20), and (5.21) when $\delta = 0.27$ are used to produce estimates of the prevalence of opiate use when the exact rate of progression to first treatment for opiate use is unknown. However when the exact rate of progression to treatment is known, $\delta = 0.23$, then Table 4.1 as discussed in chapter 4 for parameter estimates of $U(u)$ and Table 5.1 are used in combination with equations (5.14), (5.19) and (5.25) to provide esti-

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mates of the prevalence of problematic opiate use in Ireland in 2006. The estimates of prevalence of problematic opiate use in Ireland in 2006, when $t = 8$, for both situations where the exact rate of progression to treatment is unknown and known are outlined in Table 5.2 below.

Model	Exact incubation period unknown but assumed to follow $\Gamma(\alpha, \lambda)$ $\alpha \in \mathbb{N}$		Exact incubation period known, $\alpha \in \mathbb{R}$, $\alpha = 2.46$	
	$\alpha = 1$ ($\delta = 0.27$)	$\alpha = 2$ ($\delta = 0.27$)	Without Error ($\delta = 0.23$)	With Error ($\delta = 0.23$)
Case 1. Exponential Model	11,092 [8,143, 14,964]	11,123 [8,215, 14,967]	11,209 [8,518, 14,568]	10,341 [7,831, 13,484]
Rate per 1,000	3.8 [2.8, 5.2]	3.8 [2.8, 5.1]	3.9 [2.9, 5.0]	3.6 [2.7, 4.6]
Case 2. Linear Model	11,093 [7,297, 14,792]		8,568 [6,158, 10,906]	7,955 [5,789, 10,122]
Rate per 1,000	3.8 [2.5, 5.0]		2.9 [2.1, 3.8]	2.7 [2.0, 3.5]
Case 3. Quadratic Model	11,020 [8,394, 13,646]	10,837 [8,084, 13,590]	11,986 [8,792, 15,181]	11,343 [8,241, 14,446]
Rate per 1,000	3.8 [3.0, 4.7]	3.7 [2.8, 4.7]	4.1 [3.0, 5.2]	4.0 [2.8, 5.0]

Table 5.2: Estimates of the Prevalence of Problematic Opiate Use in Ireland in 2006, using equation (5.2), for the three cases of $T(u)$ in equations (5.3), (5.4) and (5.5) and $P(t)$ in equations (5.9), (5.15), (5.20), (5.10), (5.21), (5.14), (5.19) and (5.25).

The prevalence estimates presented in Table 5.2 above are for 2006, when $t = 8$. The prevalence estimates obtained are for when the exact rate of progression to treatment is unknown and when the rate of progression to first treatment is known. The estimates produced must be viewed with caution in light of the fact that they are based on data for the seven year period from 1999 to 2005 which may result in under-estimates as data prior to 1999 was unavailable for this study. However in spite of this, the 95% confidence intervals produced for some of the exponential, linear and quadratic models overlap with previously published prevalence estimates which are illustrated in Table 5.3 below.

Year	Prevalence Estimate	Confidence Interval	Rate	Source
2000	14,158	[12,884, 15,883]	5.6 per 1,000	(Kelly *et al.* 2003)
2001	14,452	[13,405, 15,819]	5.6 per 1,000	(Kelly *et al.* 2003)
2004	14,286	not supplied	not supplied	(Comiskey *et al.* 2007)
2006	20,790	[18,136, 23,576]	7.2 per 1,000	(Kelly *et al.* 2009)

Table 5.3: Summary of published prevalence estimates.

Estimates are comparable to estimates obtained by Comiskey (2001) of 13,460 for all opiate use in Dublin in 1996, when it was known that 90% of all treated opiate use was within the capital city of Dublin. In more recent times Kelly *et al.* (2003), Comiskey *et al.* (2007) and Kelly *et al.* (2009) produced estimates of prevalence and found that there was approximately 14,452, 14,286, and 20,790 opiate users in Ireland in 2001, 2004 and 2006 respectively. However it must be noted that as

stated above the estimates produced by this model are likely to be an underestimate and Kelly *et al.* (2009) expressed concerns regarding their prevalence estimates for 2006, concluding that it was probable that the estimates produced were inflated for technical reasons. Therefore it is possible that the true size of the opiate epidemic in Ireland in 2006 lies somewhere between the estimates produced in this research and the prevalence estimate of Kelly *et al.* (2009). It is also worth noting that the prevalence rates recorded in Table 5.2 are in line with the findings of the EMCDDA which has published prevalence rates for problem opioid use in European countries of between 3.6 and 4.6 cases per 1,000 of the population (EMCDDA 2009a).

5.4   Conclusions and Discussion

Prior to any prevalence estimation, the purpose of the estimate should be clearly defined. Hartnoll discusses the importance of the purpose of the estimate, i.e. "if the purpose is to assess possible treatment needs, the definition should relate to potential clients either now or in the future" (EMCDDA 1997a). The prevalence estimates in this research are based on the number of first treatment contacts for opiate use and do not include data from other sources such as police data, therefore this estimate is not representative of the true size of the opiate epidemic. The estimate does provide information on the number who may be in need of or seeking treatment. A further consequence of the choice of source for this research is that the estimate of prevalence describes the number of opiate users who may seek their first treatment in the future. These users are hidden or unknown to treatment services at present. Alternatively if first police contact or arrest data were used then the definition of the prevalence estimate should reflect this choice.

Whilst the numbers of individuals presenting for first treatment episode in Ireland appear to be decreasing overall between 1999 to 2005, the prevalence estimates of opiate use in the literature are stable. These findings raise questions regarding treatment and rehabilitation of opiate users and their future disengagement from treatment services. The rate at which individuals recover and are rehabilitated from drug use, the rate at which clients drop out of treatment and the relationship between the number of treatment episodes before they are fully recovered and rehabilitated need to be examined. Although Comiskey & Stapleton (2010) have begun to look at this in an Irish context further research would be beneficial at both national and international levels.

The method presented and implemented to estimate prevalence for the Irish situation requires knowledge of the incidence of first treatment for opiate use and the incidence of untreated opiate use. It is evident from the estimates produced in Table 5.2 that the models are not heavily dependent on knowledge of the exact rate of progression to treatment as there is not much variation in the prevalence estimates obtained regardless of the rate of progression to treatment chosen. As long as the necessary data is available on the incidence of first treatment for opiate use and the incidence of untreated opiate use, it is possible to apply the method to estimating the prevalence of problematic opiate use world-wide for policy making groups such as the EMCDDA, the WHO and the UN. Clearly knowledge of the incidence of untreated opiate use may not be known, particularly in developing countries, yet in spite of this limitation the model could be used to simulate or predict possible prevalence estimates based on different forms of the unknown incidence curve.

Prevalence could be estimated assuming constant treated incidence, for example

during a stable phase of the opiate epidemic, linearly increasing or decreasing incidence could be considered, however when implementing any model it is essential that the chosen model reflects the epidemiological situation in the country or city of application.

No one method of prevalence is without its limitations, therefore best practice would suggest that a range of different methodologies should be implemented where possible and that the range of estimates should be considered for planning purposes. This mathematical model for estimating prevalence is promising as it is robust, not heavily data dependent and is applicable to estimating the prevalence of different substances or all drug use. However further research on $T(u)$ and $U(u)$ and up to date published first treatment data would assist future researchers in achieving more accurate prevalence estimates.

5.5 Chapter Summary

A robust model for estimating the prevalence of problematic opiate use has been derived. The next chapter will use some of the prevalence estimates obtained for Ireland in order to examine the geographic spread of opiate users across Ireland.

Chapter 6

Developing and Implementing a Model for the Geographical Spread of Opiate Use in Ireland

6.1 Introduction

Describing the spread of an infection within a population as a function of time and space continues to be a basic problem in relation to epidemics, particularly opiate use. Previous chapters have discussed how opiate use, notably heroin continues to be the main problem treated drug of misuse. In spite of extensive research on the mathematical and statistical modelling of epidemics, little has been done to apply these models to the worldwide problem of spreading substance misuse. Illegal drug use is clearly a hidden phenomenon, however, viable cost-effective methods to produce regular and current prevalence and incidence estimates have been introduced, developed and applied in previous chapters. Further development of these methods to produce geographically distributed prevalence and incidence estimates is essential for the planning and provision of effective treatment services. Mathematical models first developed for infectious disease epidemiology and latterly developed for drug use can assist with these estimates. A mathematical model of geographic spread would enable treatment service providers to alter the number of places available at

treatment clinics in line with predicted client treatment requirements. The models would allow policy makers to determine where new treatment facilities could be required and make budgetary provisions for facilities for when the need arises. The specific objectives of this chapter are therefore;

- To derive a simple model for the geographical spread of opiate use.

- To simulate the spread of infectious opiate users in Ireland using available data.

- To make recommendations for planning and research based on the simulation.

6.1.1 Modelling the Geographic Spread of Opiate Use

Drug use continues to spread not only at a global level but also throughout Ireland. At the beginning of the 1980s there was an abrupt increase in opiate use in inner city Dublin. Traditionally heroin use was confined to Dublin, with the first statutory drug treatment facility established at Jervis Street hospital in 1969. Illegal drug use is no longer confined to Dublin and drug use outside Dublin has more than trebled in recent times (Condon 2004). This has resulted in the establishment of drug treatment centres throughout Ireland. The Health Research Board found that Carlow, Waterford, Louth and Wexford had the highest average incidence of treated drug use for the period between 2001 and 2006 (Alcohol and Drug Research Unit of the Health Research Board 2009).

The United Nations Office on Drugs and Crime (2004) has identified that many of the traditional systems for regulating drug use are also weakened by the trends towards globalisation which facilitates cross country trafficking. (Murray 2003b) states that the geographic spread of epidemics is less well understood and less studied

than the temporal development and control of diseases and the spread of the heroin epidemic is no exception. Clearly there is an urgent need to provide policy makers and service providers with further research into the global and national diffusion of drug use, most notably heroin use.

Research has been conducted on the spread of infectious diseases such as the spread of the Spanish flu virus, Severe Acute Respiratory Syndrome (SARS), the Black Death and rabies. However, despite the research completed, the spatial aspects of the spread of disease are regularly omitted from mathematical models (Sattenspiel 2009). Sattenspiel (2009) noted that the important questions in relation to the spread of diseases were the who, when and why. While these questions were crucial the where was equally important. Where the disease is predicted to spread is essential for determining measures to prevent further spread.

6.2   Methodology

Early research conducted by Bell & Champion (1976) suggested that the spread of drug use conformed to the diffusion model whilst Ferrence (2001) looked at how well the diffusion model fit drug use. Murray (2003b) described a diffusion model suitable for the geographic spread of a general epidemic. This diffusion model could be applied to the problem of modelling the spread of an infectious disease or indeed the spread of illegal drug use as Ryan (1969) believed diffusion originated at a single point and spread out.

Murray (2003b) considered a Susceptible Infectious Recovered or Removed (SIR) type compartment model when describing the spatial spread of rabies, where rabid foxes were considered the main cause of spatial spread. The SIR-type compartment

model is used to represent the stages of an infection and the number of classes in the model depends on the infection. An SI model would describe an infection which only has susceptible and infectious classes whereas the model for the spatial spread of rabies in foxes has susceptible, infected and infectious classes. In this model the fox population was divided into susceptible foxes, S, infected foxes, I and infectious foxes R. Although a fox is infected, I, the fox would be considered non-infectious as it only becomes rabid (infectious) and transmits the disease after a long incubation period ranging from 12 to 150 days. This simple three species (SIR) model is of particular interest as it is one of the first simple models for the spatial spread of an epidemic and in this chapter we explore its applicability to the spread of spatial spread of drug use. Murray (2003b) provided the model below;

$$\frac{\partial S}{\partial t} = aS - bS - \frac{(a-b)NS}{K} - \beta RS \quad (6.1\ a)$$

$$\frac{\partial I}{\partial t} = -bI - \frac{(a-b)NI}{K} + \beta RS - \sigma I \quad (6.1\ b)$$

$$\frac{\partial R}{\partial t} = -bR - \frac{(a-b)NR}{K} + \sigma I - \alpha R + D\frac{\partial^2 R}{\partial x^2} \quad (6.1\ c)$$

$$(6.1)$$

The model (6.1) was suggested by Murray for the spatial and temporal evolution of the rabies epizootic after considering the following assumptions.

1. The dynamics of the fox population in the absence of rabies can be approximated by the simple logistic form

$$\frac{ds}{dt} = (a - b)S\left(1 - \frac{S}{K}\right) \tag{6.2}$$

where

- a is the linear birth rate.

- b is the intrinsic death rate.

- K is environmental carrying capacity.

The parameters a, b and K are assumed constant.

2. Rabies is spread from a rabid to a susceptible fox by direct contact, usually biting. The transmission coefficient β is assumed constant and susceptible foxes become infected at an average per capita rate βR which is proportional to the number of rabid foxes present.

3. The average incubation time is $\frac{1}{\sigma}$, infected foxes become rabid at an average per capita rate σ.

4. The average duration of the disease is $\frac{1}{\alpha}$, rabid foxes die at a per capita rate α.

5. Rabid and infected foxes continue to put pressure on the environment and die of causes other than rabies; although the effects are small they are included for completeness.

6. Foxes are territorial and divided the countryside into non-overlapping ranges.

For now the equation (6.1 c) is of interest and within this chapter it will be developed and implemented for the first time to describe the geographic spread of infectious opiate users in Ireland. We considered this equation plausible to model the geographic spread of infectious opiate use as the model is based on a diffusion model

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suitable for the geographic spread of a general epidemic and is therefore not restricted

to a particular species or epidemic. Producing a valid model to describe the spatial

spread of infectious drug users particularly opiate use in Ireland is essential, but it

must be noted that the model is not restricted to one disease or drug type.

6.3   A Basic Model of the Spatial Spread of Infectious Opiate Users

The spatial spread of infectious opiate users can be expressed by:

$$\frac{\partial R}{\partial t} = [\gamma - (\mu + \delta_1 + \delta_2 + \rho)]R + D\frac{\partial^2 R}{\partial x^2}, \tag{6.3}$$

which is a partial differential equation based on equation (6.1 c) of Murray's model,

with the boundary conditions,

$$R(0, t) = A \text{ and } R(L, t) = B, \tag{6.4}$$

where A and B are the number of infectious opiate users at the starting point and at

L kilometres from the starting point. A partial differential equation is a differential

equation involving an unknown function of several independent variables containing

at least one partial derivative of some variable. The order of a partial differential

equation is the order of the highest derivative which appears in the equation. The

partial differential equation (6.3) must be solved for $R(x, t)$ which is the number of

infectious individuals in the population at a location per unit time. For the purpose

of this work an infectious individual is considered to be an individual who has been

using drugs and immediately has the potential to initiate susceptible individuals to

drug use. Drug users in treatment are not considered to be infectious as it is widely

recognised that drug-users in treatment are not considered to initiate new users (Cox & Comiskey 2007). The model parameters are described below.

- γ: The proportion of the general population that will turn fifteen in the modelling time period. The proportion of the population that turn fifteen is chosen in line with the EMCDDA (2009b) recommendation that the age range for the whole adult population is 15-64 years.

- μ: The natural death rate of the general population.

- δ_1: A removal rate that covers the natural recovery rate of drug users not in treatment.

- δ_2: A removal rate that covers drug users successful completion of treatment.

- ρ: The probability per unit time of a drug user entering treatment for problem drug use.

- D: The diffusion coefficient is a measure of the rate at which an infectious opiate user moves location.

Equation (6.3) is similar in form to the problem in physics of the spread of heat through a bar. As the spread of infectious opiate users in an area is of interest in this research the partial differential equation (6.3) is solved for $R(x,t)$ using the mathematical package Maple. The pdsolve command in Maple solves the partial differential equation (6.3) such that the boundary conditions are satisfied to give,

$$R(x,t) = \left[\frac{\exp\left(\sqrt{\frac{\mu+\delta_1+\delta_2+\rho-\gamma}{D}}(L-x)\right)}{-1+\exp\left(2\sqrt{\frac{\mu+\delta_1+\delta_2+\rho-\gamma}{D}}L\right)} \right] \left[B\exp\left(2\sqrt{\frac{\mu+\delta_1+\delta_2+\rho-\gamma}{D}}x)\right) \right.$$

$$- (A-B)\exp\left(2\sqrt{\frac{\mu+\delta_1+\delta_2+\rho-\gamma}{D}}(-2x+L)\right)$$

$$\left. + A\exp\left(\sqrt{\frac{\mu+\delta_1+\delta_2+\rho-\gamma}{D}}L)\right) \right]. \tag{6.5}$$

The pdsolve command looks for the most general solution to the given partial differential equation such that the boundary conditions are satisfied. The next section of this chapter estimates the parameters of equation (6.5) in order to investigate the geographical spread of opiate users in Ireland.

6.4 Numerical Simulation of the Basic Model

Before the geographical spread of opiate users can be investigated using equation (6.5) the parameters of the model must be estimated. Once again the difficulty associated with estimating parameters for these models due to the nature of drug use must be reiterated. In this section the Irish parameters for the basic model are estimated adopting the same technique used by White (2008) for her models of problem opiate use. White (2008) outlined the difficulties assigning values to the parameters in her models and some of the difficulties which are similar for this model are outlined below.

6.4.1 Estimates of the Irish Parameters for the Basic Model

To estimate the natural death rate, μ, White (2008) uses the Life Tables produced by the Central Statistics Office (CSO) in Ireland. The Life Tables are constructed

using the most recent census population figures and the number of deaths at each age from the most Vital Statistics annual reports. Both the population figures and the number of deaths at each age are combined in order to calculate the current life expectancy at birth for men and women. The most recent Life Tables available were for the years 2005-2007, the average life expectancys at birth for men and women were 76.8 years and 81.6 years respectively, therefore the average life expectancy is 79.2 years. The natural death rate, which includes drug related deaths, for this model, μ, is then taken to be $\frac{1}{79.2} = 0.013$.

The parameter γ is estimated using population figures from the 2006 census. The number of individuals aged fourteen that will potentially turn fifteen in the modelling time period and the total population are both required for 2006. In 2006, there were 57,105 individuals aged fourteen recorded in the census and the total population for the same year was 4,239,848. The proportion of the general population that will turn fifteen in the modelling time period, γ, is $\frac{57,105}{4,239,848} = 0.013$.

The natural recovery rate, δ_1 is defined as by White & Comiskey (2007) as the rate at which infectious individuals stop using drugs without treatment. Throughout this research the hidden nature of drug use has been emphasised and all the estimation techniques suggested depend on the known incidence of treatments therefore, as yet, there is no technique available to estimate the natural recovery rate of drug users. For the purpose of this research, the assumption made by White (2008) of $\delta_1 = 0.10$ is also used. This assumption is based on Kaya *et al.* (2004) finding that the majority of drug users begin and stop drug use within one year, having never entered treatment and a drug-using career duration of ten years.

The removal rate, δ_2, represents treatment success. For this research it is as-

sumed that an individual who is successfully treated is cured and therefore is no longer infectious i.e. no longer has the potential to spread opiate use. As discussed in chapter 3 the National Drug Treatment Reporting System (NDTRS) is a comprehensive database for drug treatment in Ireland, therefore, in order to estimate the treatment success parameter for 2006, Table 6.1 below includes details of treatment cases by treatment status.

Year	New Cases	Previous Cases	New and Previous Cases	New Cases	Previous Cases
	(n)	(n)	(n)	%	%
2003	759	2,190	2,949	26	74
2004	654	2,108	2,762	24	76
2005	722	2,281	3,003	24	76
2006	912	2,237	3,149	29	71
2007	1032	2404	3,436	30	70

Table 6.1: Cases presenting for treatment for opiate-use in Ireland 2003-2007, by known treatment status. Source: Alcohol and Drug Research Unit of the Health Research Board (2009)

The rate of successful treatment is estimated from Table 6.1 and is taken as one minus the probability of relapsing, which is denoted σ. The relapse probability, σ is the average number of previously treated cases per unit time. Using the figures from Table 6.1, σ for the year which we are modelling the geographic spread of opiate use, 2006, is 0.71, therefore $\delta_2 = 1 - 0.71 = 0.29$.

As little is known about the movements of an infectious drug user due to hidden nature of the activity the method used by Murray (2003b) to estimate D the diffusion

coefficient is assumed for simulation purposes. The distance between the starting location of the infectious opiate users and the location of interest and the average latency period to estimate D are used. Therefore D which is measured in km^2/year is expressed as:

$$D \approx \frac{1}{N} \sum_{j=1..N} \frac{(\text{straight line distance from the start}^2)}{4 \times (\text{time from the start in days})},$$

where N is the total population involved. The total population figure for 2006, N taken from the census figures is 4,239,848. The time from the start is taken to be the average latency period of 4.3 years as estimated in chapter 3 which is the equivalent of 1570.5 days.

The per capita probability per unit time that an individual is no longer infectious due to commencing treatment, ρ, depends on all treatments cases for opiate use in 2006, as presented in Table 6.2 and the estimates of all opiate users in Ireland in 2006.

Year	All Cases
	(n)
2003	3029
2004	2863
2005	3094
2006	3280
2007	3575

Table 6.2: Total number of cases presenting for treatment for opiate-use in Ireland 2003-2007. Source: Alcohol and Drug Research Unit of the Health Research Board (2009).

Thus ρ is calculated by dividing the number of all opiate treatments in 2006, 3280, by the number of all opiate users in Ireland in 2006 which was estimated in chapter 5. Thus several values are calculated for ρ, based on the prevalence estimates in Table 5.2 in chapter 5. Table 6.3, 6.4 and 6.5 summarise the boundary values and parameters that will be used when simulating the geographic spread of infectious opiate users in Ireland in 2006 using equation (6.5).

6.5 Simulation Results for the Spread of Infectious Opiate Users in Ireland

For simulation purposes Dublin is considered to be the starting point, $x = 0$ and Wexford is considered to be location $x = 150$ as Wexford is approximately 150 km from Dublin. Using the solution obtained for equation (6.3) and the parameters estimated in Tables 6.3, 6.4 and 6.5 the geographical spread of infectious opiate users between Dublin and Wexford is presented in Figure 6.1.

Estimates of All Opiates Users	ρ	Estimates of All Opiate Users	ρ
11,092	0.30	11,123	0.29
11,209	0.29	10,341	0.32
11,093	0.30	8,568	0.38
7,955	0.41	11,020	0.30
10,837	0.30	11,986	0.27
11,343	0.29		

Table 6.3: Estimates of all opiate use in Ireland in 2006 from Table 5.2 with estimates of ρ .

Parameter	Values
μ	0.013
γ	0.013
δ_1	0.10
δ_2	0.29
D	35.8

Table 6.4: Estimates of parameters for basic model.

The boundary conditions are outlined in Table 6.5 for $x = 0$ and $x = L$ when $L = 150$. To estimate values for A the number of infectious opiate users in Dublin in 2006, the estimates of prevalence of all opiate users in Ireland from chapter 5, Table 5.2 are considered. Kelly et $al.$ (2009) found that 72% of all opiate users in 2006 resided in Dublin therefore $A =$ all opiate users $\times 0.72$. Comiskey et $al.$ (2010) estimated that there were approximately 1,000 opiate users in the south east region

in 2006, therefore B for all simulations is 1,000.

$R(0,t) = A$	$R(150,t) = B$	$R(0,t) = A$	$R(150,t) = B$
A	B	A	B
7,986	1,000	8,009	1,000
8,070	1,000	7,446	1,000
7,987	1,000	6,169	1,000
5,728	1,000	7,934	1,000
7,803	1,000	8,630	1,000
8,167	1,000		

Table 6.5: Boundary conditions.

The spread of opiate users, $R(x,t)$, from Dublin to Wexford in 2006 is illustrated in Figure 6.1 for all of the estimates of the number of opiate users in chapter 5.
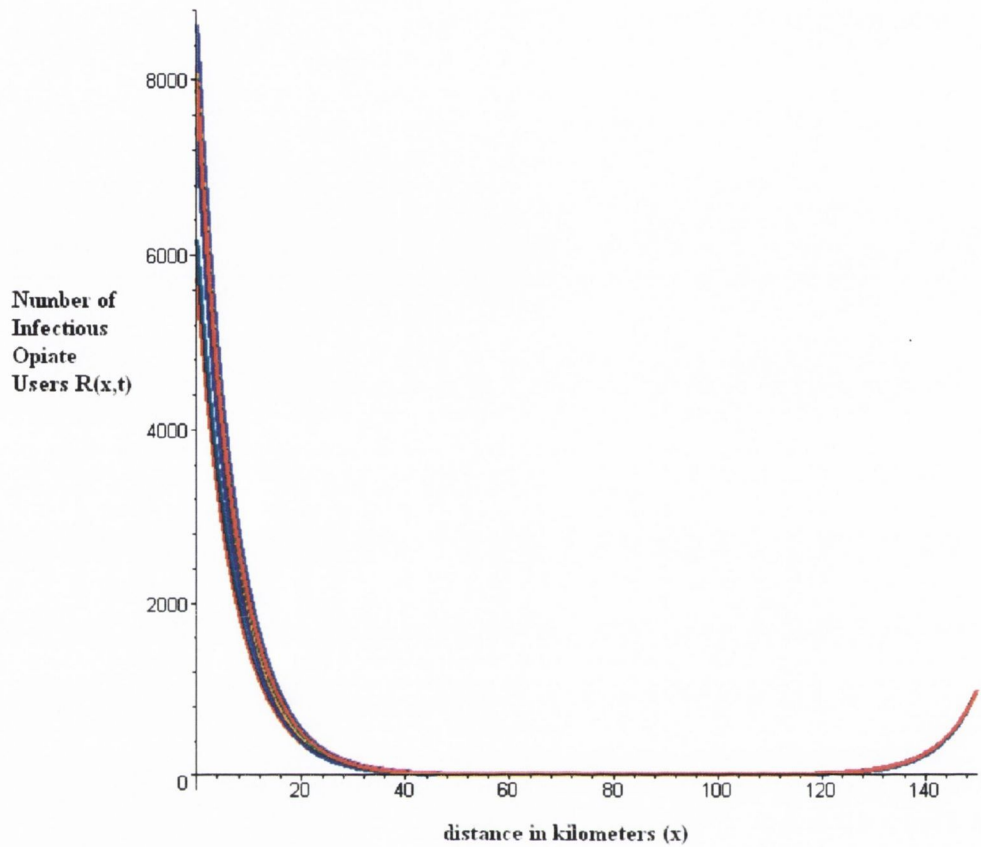
Figure 6.1: $R(x,t)$ the number of infectious opiate users at location x in 2006.

As the numbers of opiate users estimated were consistent the spread is very similar for all values of A.

6.6 Conclusion and Discussion

Figure 6.1 illustrates a decreasing pattern of infectious opiate users as x increases i.e. the further distance travelled from Dublin, but as x gets closer to 150, as we approach Wexford a pattern of increasing numbers of infectious opiate users can be seen. This finding would be expected as problem drug use has long been perceived

as a city problem. The model illustrates a greater concentration of opiate users close to the two urban areas as expected. Whilst the model used does offer some insight into the spread of infectious opiate users in Ireland, it is a very basic model and by altering the boundary conditions and parameters in line with data available on the number of opiate users at a location x patterns of spread from Dublin to other cities or areas could be illustrated.

The model presented is very much an initial model illustrating the possibilities of developing such models for future research and the model should be viewed as a foundation on which to build a more complex model of the geographical spread of opiate use not only the spread of opiate users. Once again the hidden nature of opiate use, and indeed all drug use, hinders the development of models. There are many suggestions which can be made with regard to future work for this model, all of which would benefit from a more in-depth knowledge on the dynamics of the hidden activity of drug use such as how infectious opiate users interact with the susceptible population or the size of the susceptible population could be modelled after considering an opiate users social network. A model similar to Murray's in equation (6.1) could be applied in the future but would require research on elements of the model such as the susceptible population, the infected population and the diffusion coefficient to name a few.

Despite the limitations of this models it is still beneficial to planners and treatment service providers as it would permit them to apportion funding and resources for drug treatment based on the number of infectious drug users in an area. As it is not practical to allocate treatment facilities to every town where an infectious drug user resides this model would allow planners to distribute the available resources

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within feasible travelling distance for the individuals that would be using them.

6.7   Chapter Summary

A basic model for the spread of infectious opiate users in Ireland in 2006 has been derived and used to simulate the hypothetical spread of infectious opiate users from Dublin to Wexford. The final chapter summarises the results obtained in the thesis with suggestions for further work.

Chapter 7

Conclusions and Further Work

7.1 Introduction

This thesis applies disease modelling and size estimation techniques to opiate use in Ireland. This chapter highlights the results obtained in the thesis in view of the objectives of the thesis and the specific aims outlined in each chapter. The objectives of this research were:

- To derive an effective model to estimate the hidden incidence of opiate use when the exact rate of progression to treatment was unknown.

- To solve the model derived and produce estimates of the hidden incidence of opiate use in Ireland when the exact rate of progression to treatment is not known.

- To obtain data on the times taken by opiate users to progress to their first treatment.

- To derive suitable probability distributions to the times to first treatment for opiate users and hence estimate the so called "incubation period" from first opiate use to first treatment.

- To take the known rate of progression to treatment as estimated and implement it in the model derived to estimate the incidence of opiate use.

- To provide the first mathematical analytical solutions to the back calculation model when the exact rate of progression to treatment is known and the parameters of the incubation period are $\in \mathbb{R}$.

- To use the analytical solutions obtained to produce estimates of the hidden incidence of opiate use when the exact rate of progression to treatment is known.

- To derive the first integral model to estimate the prevalence of opiate use.

- To implement the prevalence model derived and produce estimates of the prevalence of opiate use.

- To develop and implement a model for the geographical spread of infectious opiate users and apply it to Ireland for the first time.

Chapter 1 describes the modelling process and gives a brief history of mathematical modelling in epidemiology. It also details integral equations which are the basis for the subsequent models derived. Chapter 1 also describes the background to problem drug use, specifically opiate use and details some of the mathematical models previously applied to estimating problems in illegal drug use.

7.2 Conclusions

In chapter 2 the back calculation model was described and analytically solved for a range of forms of the treated incidence of opiate use when the exact rate of progression to treatment is unknown. The solutions obtained were then applied to the

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problem of estimating the incidence of opiate use in Ireland. Chapter 3 describes the data obtained on times to first treatment for opiate users and fits Gamma and Weibull probability distributions to the data resulting in an estimate of the exact rate of progression to first treatment. Chapter 4 takes the exact rate of progression to treatment model, applies it to the back calculation model for the hidden incidence of opiate use and analytically solves for the first time the equation for a range of forms of treated incidence. The solutions obtained were then used to produce estimates of the hidden incidence of opiate use when the exact rate of progression to treatment is known. Chapter 5 derives an integral equation model to estimate the prevalence of opiate use based on the models derived for the hidden incidence of opiate use. The models were solved and estimates of the prevalence of opiate use were obtained for situations where the exact rate of progression to treatment is unknown and known, for Ireland in 2006. Chapter 6 derives a partial differential equation for the geographical spread of opiate users in Ireland for 2006, discusses and implements techniques used to estimate the model parameters and uses the prevalence estimates derived in chapter 5 in order to simulate the hypothetical geographic spread of opiate use from Dublin to Wexford.

7.3   Relevance of Work

Researchers internationally are interested in determining the true size of the opiate and indeed drug epidemic. This research addresses this need by providing epidemiologists, health care workers, researchers and policy makers with the tools necessary to estimate new hidden cases of opiate use, all cases of opiate use and the spread of infectious opiate use.

The first estimates of the hidden untreated incidence of opiate use in Ireland have been produced. While the prevalence of illegal drug and opiate use has been estimated in many countries little has been done to estimate the number of new cases and hence the incidence rate of illegal drug use. The lack of data on the latency period of opiate use has been addressed and analytical solutions to the back calculation equation has been produced. The application of the solutions obtained and the models developed are not restricted to the Irish setting. These models could be applied by health care providers, epidemiologists and policy makers globally to estimate the number of new cases and the incidence rate of illegal drug use depending on the availability of timely and accurate data. The availability of these models to estimate the incidence would enable service providers to ensure adequate treatment services will be available to meet future treatment requirements. Service providers could use the models to anticipate the number of first treatment contacts who have the potential to avail of treatment services in the future.

The models developed for the rate of progression to first treatment could be applied in a similar manner to international data on times to first treatment for opiate use. However, application of the models is not restricted to data on opiate use nor is it restricted to first treatment data. The models could be used by service providers, policy makers and epidemiologists nationally and internationally to establish the average time to first treatment for a range of different illegal substances. These models are essential to estimate incidence however, they are also necessary to ensure treatment services are established in a timely manner. The models allow service providers to prepare for future treatment needs as they raise awareness of the proportion of the opiate using population who will present for treatment at

a specified time in the future. Using these models will ensure government agencies apportion and utilise funding for treatment services in an appropriate manner which is particularly relevant in the current economic climate where funding cuts are occurring at an increasing rate.

There is no shortage in availability of models to estimate the prevalence of illegal substance however, no model is without limitations. Previously models to estimate prevalence have been costly and time-consuming to implement. The robust model developed in this research is applicable to a range of different substances and can be applied globally. The model presented in this study can be applied by policy-making groups such as the WHO and the EMCDDA to estimate the true size problematic drug-use world wide provided the necessary data is available.

Finally a model for the spread of infectious opiate use was introduced in this thesis. While the model is only a very basic model it gives service providers an insight into where problem drug use is likely to spread to in the future. This knowledge of the spread of opiate use enables health care providers and funding agencies to introduce the appropriate treatment services in locations within feasible travelling distances for potential service users.

7.4   Discussion and Further Work

The models presented in chapters 2, 4 and 5 could be utilised to produce estimates of any problematic drug use in any specified location providing the necessary data on first treatment contacts and rates of progression to treatment were available. The model in chapter 6 is a basic one and could be built upon in the future to produce a more complex model of the geographic spread of opiate use to include susceptible

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and infected populations. The model would benefit from further research, any of the following could be a starting point for further research:

- The drug using process.

- The social networks of drug users.

- The initiation process to opiate use.

- The length of time it takes for an infected opiate user to become infectious.

In light of the difficulties regarding parameter estimation in chapter 6 and having only one estimate of the number of infectious opiate users in Wexford it would be constructive to consider investigating if a spatial element could be included in the prevalence models produced in chapter 5. In order to produce a more comprehensive model for the geographical spread of opiate use it would be favourable to consider adding a spatial element to all models derived for the prevalence and incidence in the future. The main limitation of all the models demonstrated is a lack of published data on drug use, mainly as a result of the hidden nature of the activity. These models will enable researchers, policy makers and service providers to make initial estimates of the size and spread of the epidemic and the potential number of future treatment contacts. However should the aims of the Department of Community, Rural and Gaeltacht Affairs (2009) be fulfilled then up to date data would be recorded and documented resulting in the production of current and regular prevalence and incidence estimates for opiate use and indeed any other problematic drug of misuse.

Models for the prevalence, incidence and geographical spread of opiate use have been derived and implemented and further work has been suggested however it is by

no means exhaustive. Patterns of drug use and treatment needs and availability are constantly changing particularly with the current economic downturn, models need to reviewed and updated as data becomes available in order to allocate increasingly scarce resources in the most effective manner.

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