Irish Epidemiology Modelling Advisory Group,
Advisory Group to NPHET
Technical Notes

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Note from Prof. Philip Nolan, IEMAG Chair

Introduction

The Irish Epidemiological Modelling Advisory Group (IEMAG) was formed on 11 March 2020 to provide statistical and mathematical modelling support and advice to the Chief Medical Officer and the National Public Health Emergency Team (NPHET). The remit of IEMAG includes:

- gathering evidence and monitoring the epidemiological characteristics of the COVID-19 outbreak in Ireland and the pandemic internationally; and
- developing epidemiological models to forecast the COVID-19 outbreak in the Republic of Ireland, monitoring the impact of public health interventions, and modelling probable scenarios for numbers of new cases of COVID-19 over time.

IEMAG is has published a set of technical notes to inform other scientists, epidemiologists statisticians and mathematicians of our approach, and to help refine and enhance our techniques and models. These notes are of necessity technical in nature.

Mathematical models of SARS-CoV-2 infection

A mathematical model of an epidemic is a tool to help us better understand the epidemic as it evolves, to examine possible scenarios for strategic and operational planning, and to support risk assessment and public health decisions. Statistical and modelling approaches have significant and important limitations. These limitations are well understood by NPHET and key decision makers.

The central model used is a population-based SEIR model[1]. This is a robust, widely-utilised and well-understood approach to modelling infectious disease, and as such could be developed and deployed quickly. The model divides the population into compartments, starting with those *susceptible* to the virus (the S compartment); at the outset, for a novel virus where there is no immunity in the population, the entire population is susceptible. The model is seeded with a small number of individuals who are infected with the virus and as a result some of the population become exposed to the virus and are assigned to the *exposed* (E) compartment. These individuals are not yet infectious: the virus is replicating in their bodies, but they are not yet shedding virus. However, after the latent period (3-4 days) the individual becomes infectious and is assigned to the *infectous* (I) compartment for the duration of the infectious period (the model assumes an average infectious period of 5-9 days, which is typical, though individuals may remain infectious for up to 14 days and sometimes longer). Finally, at the end of the infectious period the individual is *removed* from the model (to the R compartment) on the basis that they are immune to further infection.

The dynamics of the model are driven by the dynamics of viral transmission, expressed as a set of differential equations, and in particular the *reproduction number* (R). An intuitive way to think of R is as the average number of infections caused from each new case. Of course some cases will lead to many secondary infections, and some may lead to none. The quoted average can be useful, since values bigger than 1 indicate a situation where we expect substantial growth in the future number of cases, whereas values close to zero indicate that it is expected to see many fewer future cases than currently are incident.

It is important to distinguish between basic reproduction number (R_0) and effective reproduction number (R)

- The basic reproduction number, R_0, is the expected number of additional cases that are generated, on average, by a single but typical case, over the course of its infectious period, in an otherwise uninfected population, where the entire population is susceptible and no public health interventions are in place. It is characteristic of the early phase of an unmitigated epidemic of a new emerging virus where there is no prior immunity in the population.
- The effective reproduction number, R, is a dynamic estimate of the average number of secondary cases generated by a single but typical case, over the course of its infectious period, in a population where an outbreak is ongoing and there are changes in the level of contact between people or the level of immunity in the population.

Reproduction number is a characteristic of the virus *and* the population. The number of other people likely to be infected by any given infectious individual is proportional to:

- the number of close contacts between the infectious individual and susceptible contacts;
- the probability that any given contact leads to infection;
- the duration of the infectious period.

Reproduction number, and hence the rate at which a virus spreads through a population, can be reduced by reducing the number of contacts, or by reducing the probability that a contact leads to infection (by hygiene, distancing, or barriers). Reproduction number is an important parameter in SEIR models of disease transmission[*], and estimates of effective reproduction number are valuable in monitoring our progress in mitigating or suppressing the epidemic.

The usefulness of a model of an infectious disease depends heavily on assumptions about how the virus is transmitted from person to person and how the disease develops and propagates. SARS- CoV-2 is a new virus, and COVID-19 a novel disease. IEMAG immediately established an epidemiological parameters sub-group to review and critique the available research as it emerged, providing very high-quality evidence in a timely manner on the dynamics of viral transmission and the nature of the disease. The technical note[2] is a summary of this work, evaluating current research on the epidemiology of COVID-19 and providing best estimates of the important parameters, which were then used to inform the development of the mathematical models and their calibration.

The overall model used by IEMAG is summarised in diagrammatic form in Figure 1. The outputs of the SEIR model are used to estimate demand for hospital and critical care, and mortality, based on data from the European Centres for Disease Control and calibrated against the experience of the epidemic in Ireland.

We are currently working on:

[*] The relevant parameter in the SEIR model is β. R is the average number of other individuals infected by a typical infectious case over the full course of the infectious period. β is the number of other individuals infected *per unit time*. R = β.D where D is the duration of the infectious period.

a) an age-cohort version of the SEIR model, to allow for differences in susceptibility and infectiousness between children and adults, and different patterns of social mixing within and between age cohorts; and
b) an agent-based model, examining in finer detail the impact of different patterns of activity on viral transmission

Estimation of reproduction number (R)

We present technical notes on the approaches used to estimated effective reproduction number (R_e) or time-dependent reproduction number (R_t) over the course of the epidemic. This is a difficult parameter to estimate, and we are currently using several approaches to cross-check and triangulate. The SEIR model can be used to infer R; the technique developed by Wallinga and Teunis (2004)[3] provides an estimate of time-dependent reproduction number[4], and we have also used the approach introduced by Flaxman *et al.* (2020)[5] to examine the effect of interventions on reproduction number[6]. These Bayesian methodologies have been further refined [7] and are implemented through the epidemia package [8]

We have also developed an approach to estimating R_e using generalised additive methods, applied to individual time series and merged estimates using multiple time series. A technical note on this technique is being prepared.

County-level estimates of incidence for the first phase of the pandemic in Ireland

The spread of SARS-CoV-2 across Ireland in the period February to June 2020 was uniform, with the peak incidence and the time to peak incidence being different in different parts of the country. We have estimated the profile of the outbreak for each county using a Bayesian hierarchical Poisson model, fitted to the confirmed case data per county, where the mean parameter for each county is modelled using a Gompertz curve[9]. The model can be used to monitor the county level daily incidence per 100,000 population.

Hospital service demand and capacity model

We have, through colleagues in the Economic and Social Research Institute (ESRI), developed a hospital service demand and capacity model[10]. The model is a deterministic simulation that starts with county-level predictions (from the SEIR model described above) of the projected number of cases diagnosed each day with SARS-CoV-2 infection under a range of possible epidemiological scenarios. To project the service demand associated with a given epidemic scenario, assumptions are required about the numbers of patients who will experience varying levels of severity of the illness and receive relevant levels of treatment. The main required assumptions are age- and sex-specific probabilities of admission to hospital and critical care, as well as average length of stay for each stage of the main care pathways. These assumptions are made based on the experience of the pandemic to date in Ireland as reported by the Health Protection and Surveillance Centre (HPSC). Given these assumptions, the model predicts the number of cases in each county requiring critical or non-critical acute hospital care on each day of the projection period.

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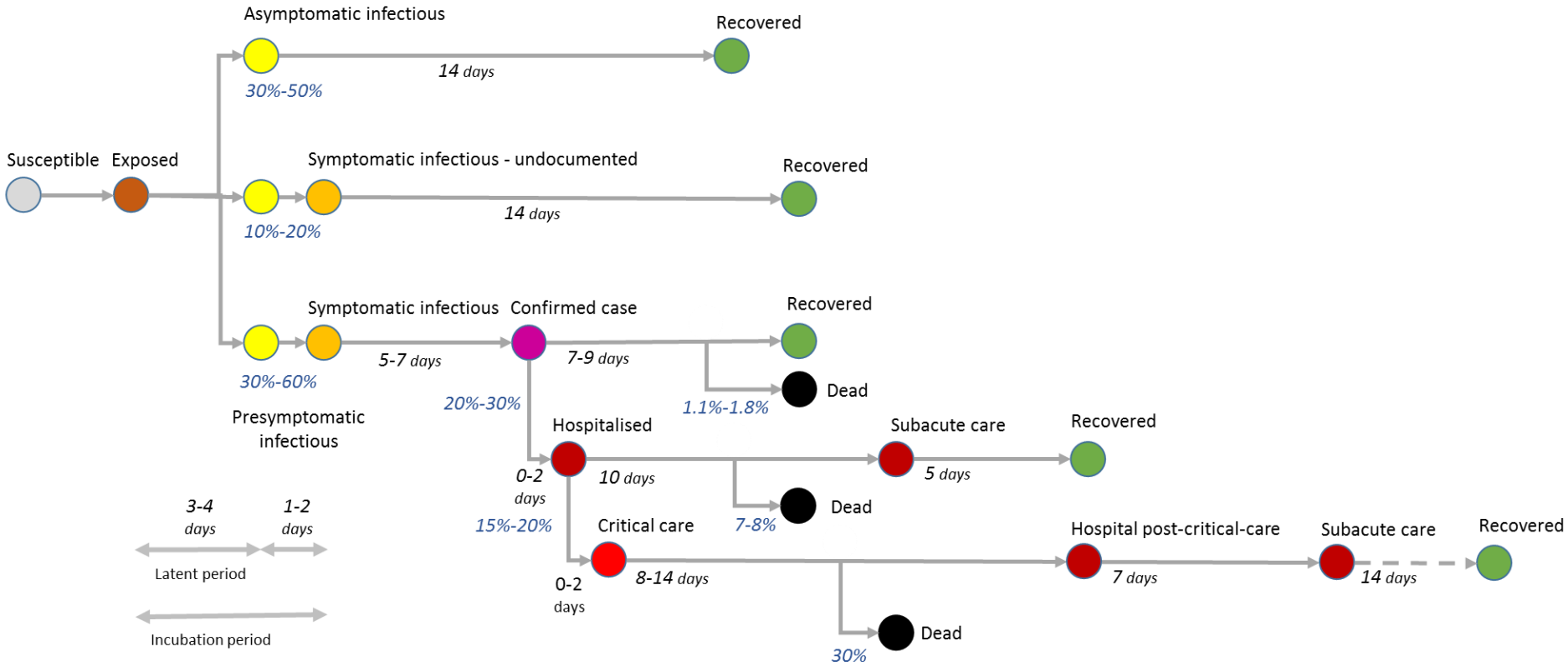

Figure 1: Model of disease and care: The parameters here are clinical, and used to estimate healthcare demand from the outputs of the SEIR model. The SEIR model uses wider and in some cases different estimates for these parameters. The hospitalisation, intensive care admission, and mortality rates are the estimates, based on ECDC rapid risk assessments and early experience of the pandemic, used to generate scenarios for the April to June period. Given the very strong testing regimen in place now, many more mild and asymptomatic cases are being detected, and our current estimates of these parameters are considerably lower.

References

[1] A population-based SEIR model for COVID-19 scenarios. IEMAG Technical Note 1, 11 May 2020.

[2] COVID-19 Epidemiological parameters – summary note. IEMAG Technical Note 2, 13 May 2020

[3] Wallinga J & Teunis, P (2004) Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am J Epidemiol. 160: 509-10

[4] Statistical estimates of time-dependent reproduction number. IEMAG Technical Note 4, forthcoming

[5] Flaxman, S *et al*. (2020a) Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries. MRC Centre for Global Infectious Disease Analysis COVID-19 Report 13. 30 March 2020

[6] Estimation of the effective reproduction number (Rt). IEMAG Technical Note 3, 20 May 2020

[7] Flaxman, S *et al*. (2020b) Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature 584: 257–261. https://doi.org/10.1038/s41586-020-2405-7

[8] https://imperialcollegelondon.github.io/epidemia/articles/introduction.html#ref-Flaxman2020

[9] A Hierarchical Model for Monitoring County Level Incidence, IEMAG Technical Note 5, 27 May 2020

[10] COVID-19 Hospital Utilisation Planning model, IEMAG Technical Note 6, 24 September 2020