

Preface

These lecture notes collect the material used for the talks delivered by Fred Brauer and Carlos Castillo-Chavez in the CBMS workshop *Mathematical Epidemiology with Applications* funded by the National Science Foundation and held at East Tennessee State University (ETSU) from July 25–29, 2011. The goal of the lectures was to reach *all participants*, a population that includes researchers with backgrounds in the biological, epidemiological, mathematical, and medical sciences as well as individuals involved in the development, implementation, and evaluation of public health policy. It was assumed that participants were cognizant of the value and utility of mathematical models in the study and control of infectious diseases because of their use to increase our understanding of disease dynamics, their value in the evaluation of possible prevention/intervention/control policies, their key role in the exploration of “what if” scenarios systematically, and their use in assessing and/or reducing the levels of uncertainty naturally associated with the unpredictability of disease outbreaks, disease severity, and disease evolution.

These notes describe a variety of topics, but are not meant to present a complete portrait of mathematical epidemiology. The interested reader may wish to consult other sources, such as the books [2, 5, 9], compilations of lectures [1, 4, 10], chapters in books on mathematical biology [3, 12], and the survey paper [8]. The notes were written using *primarily* the published research of both authors, classical articles, and research or expository articles that we have found useful.

Diseases have been important in shaping the course of history. The book [11] describes some of the influences of the impact of communicable diseases on history since ancient times. Disease dynamics biblical references include the description in the book of Exodus of the plagues that Moses brought down upon Egypt and the decision of Sennacherib, the king of Assyria, to abandon his attempt to capture Jerusalem about 700 BC because of the illness of his soldiers (Isaiah 37, 36–38).

The fall of empires has been attributed directly or indirectly to epidemic diseases. In the 2nd century AD the so-called Antonine plagues (possibly measles and smallpox) invaded the Roman Empire, causing drastic population reductions and economic hardships leading to disintegration of the empire which facilitated invasions. The Han empire in China collapsed in the 3rd century AD after a similar sequence of events. The defeat of a population of millions of Aztecs by Cortez and his 600 followers was facilitated by an outbreak of smallpox that devastated the Aztecs but had almost no impact on the invading Spaniards. Smallpox spread southward to the Incas in Peru and was an important factor in the success of Pizarro’s invasion a few years later. Smallpox was followed by other diseases such as measles and diphtheria imported from Europe to North America. In some regions, the indigenous populations were reduced to one tenth of their previous levels by

disease invasions. Between 1519 and 1530 the Indian population of Mexico was reduced from 30 million to 3 million.

The Black Death (probably bubonic plague) spread from Asia throughout Europe in several waves during the 14th century, beginning in 1346, and is estimated to have caused the death of as much as one-third of the population of Europe between 1346 and 1350. The disease recurred periodically in various regions of Europe for more than 300 years, notably as the Great Plague of London of 1665–1666. It gradually withdrew from Europe. As the plague struck some regions harshly while avoiding others, it had a profound effect on political and economic developments in medieval times. In the last bubonic plague epidemic in France (1720–1722), half the population of Marseilles, 60 percent of the population in nearby Toulon, 44 percent of the population of Arles, and 30 percent of the population of Aix and Avignon died, but the epidemic did not spread beyond Provence.

Many of the early developments in the mathematical modeling of communicable diseases are due to public health physicians. The first known result in mathematical epidemiology is a defense of the practice of inoculation against smallpox in 1760 by Daniel Bernoulli, a member of a famous family of mathematicians (eight spread over three generations) who had been trained as a physician. The first contributions to modern mathematical epidemiology are due to P.D. En'ko between 1873 and 1894 [6], and the foundations of the entire approach to epidemiology based on compartmental models were laid by public health physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, and W.O. Kermack between 1900 and 1935, along with important contributions from a statistical perspective by J. Brownlee.

The development of mathematical methods for the study of models for communicable diseases led to a divergence between the goals of mathematicians, who sought broad understanding, and public health professionals, who sought practical procedures for management of diseases. While mathematical modeling led to many fundamental ideas, such as the possibility of controlling smallpox by vaccination and the management of malaria by controlling the vector (mosquito) population, the practical implementation was always more difficult than the predictions of simple models. Fortunately, in recent years there have been determined efforts to encourage better communication between mathematicians, so that public health professionals can better understand the situations in which simple models may be useful and mathematicians can recognize that real-life public health questions are much more complicated than the worlds generated with simple models.

The philosophy behind the set of lectures by Fred Brauer may be partially characterized as one that focuses on the mathematical analyses of classical epidemic models from a perspective shaped not only by mathematical contributions to the field of epidemiology but also by the context of specific diseases such as influenza or SARS. Castillo-Chavez's lectures are driven by his desire to address *naturally* emerging epidemiological questions, that is, those that typically arise in the study of the dynamics of specific diseases. His lectures, complementary to those given by Fred Brauer, provide a personal overview on the way that Castillo-Chavez, as a member of a practitioner class of epidemiologists, broadly understood to include computational and theoretical biologists, public health experts, and evolutionary biologists, approaches the solution of the scientific challenges that emerge from the study of disease dynamics over multiple temporal and spatial scales, dynamics most often driven or shaped by evolving levels of heterogeneity, the kind *normally* found in co-evolving biological populations. Thus, in particular, there are two chapters on influenza, the first concerned with the basic structure of a single outbreak and the second

viewing influenza in a broader context and including such questions as cross-immunity between different strains.

Communicable diseases such as measles, influenza, or tuberculosis are important in modern life. In this monograph, we will be concerned both with sudden disease outbreaks and endemic situations, in which a disease is always present. The AIDS epidemic, the recent SARS epidemic, recurring influenza, and the re-emergence of tuberculosis are events of concern and interest to many people. Every year millions of people die of measles, respiratory infections, diarrhea, and other diseases that are easily treated and not considered dangerous in the Western world. Diseases such as malaria, typhus, cholera, schistosomiasis, and sleeping sickness are endemic in many parts of the world. Further, the impact of sexually transmitted disease on the reproductive health of women, the devastating impact of sexually transmitted HIV on the young and very young all over the world, and the synergistic interactions between HIV and communicable diseases like tuberculosis or vector-transmitted diseases like malaria show that the effects of high disease mortality on mean life span and of disease debilitation and mortality on the economy in afflicted countries are considerable.

In the face of a disease outbreak it is not possible to do experiments comparing the effects of different management strategy, and predictions based on mathematical models may be essential when it comes down to addressing the impact of communicable diseases. Models must be based on some understanding of the etiology and epidemiology of the disease in question and in some instances on the social and behavioral dynamics of the populations affected. Generally, diseases transmitted by viral agents, such as influenza, measles, rubella (German measles), and chicken pox, confer immunity against reinfection. We will describe *SIR* (susceptible–infectious–recovered) models for such diseases. Diseases transmitted by bacteria, such as tuberculosis, meningitis, and gonorrhoea, confer no immunity against reinfection, and we will describe *SIS* (susceptible–infectious–susceptible) models for such diseases.

Other diseases, such as malaria, are transmitted not directly from human to human but by vectors, agents (usually insects) who are infected by humans and who then transmit the disease to humans. Heterosexual transmission of HIV/AIDS is also a vector process in which transmission goes back and forth between males and females. Diseases with vector transmission require models for both host and vector populations and the interactions between them.

The distinction between epidemic and endemic situations will be highlighted in this book. An epidemic acts on a short time scale, a sudden outbreak of a disease that infects a substantial portion of the population in a region before it disappears, usually leaving many members untouched. In an endemic situation, a disease becomes established in a population and remains for a long time. In models for epidemics one usually ignores demographic effects (births and deaths not due to disease). The justification for ignoring demographic effects is that the demographic time scale is normally much longer than the disease time scale and may therefore be neglected. Endemic situations, on the other hand, may endure for years, and it is therefore necessary to include demographic effects in models that describe their dynamics.

There are many questions of interest to public health physicians confronted with a possible epidemic. For example, how severe will an epidemic be? This question may be interpreted in a variety of ways. For example, how many individuals will be affected and require treatment? What is the maximum number of people needing care at any particular

time? How long will the epidemic last? How much good would quarantine of victims do in reducing the severity of the epidemic? Can treatment of infected individuals prevent the epidemic from spreading?

Scientific experiments are usually designed to obtain information and to test hypotheses. Experiments in epidemiology with controls are often difficult or impossible to design due to ethical questions. Sometimes data may be obtained after the fact from reports of epidemics or of endemic disease levels, but the data may be incomplete or inaccurate. In addition, data may contain enough irregularities to raise serious questions of interpretation, such as whether there is evidence of chaotic behavior [7]. Hence, parameter estimation and model fitting, a critical component of model validation, are difficult.

In the mathematical modeling of disease transmission, as in most other areas of mathematical modeling, there is always a trade-off between simple models, which omit most details and are designed only to highlight general qualitative behavior, and detailed models, usually designed for specific situations including short-term quantitative predictions. Detailed models are generally difficult or impossible to solve analytically, and hence their usefulness for theoretical purposes is limited although their strategic value may be high.

Simple models for epidemics predict that an epidemic will die out after some time, leaving a part of the population untouched by disease. This prediction holds true of models that include control measures. This qualitative principle is not by itself helpful in suggesting what control measures would be most effective in a given situation, but it implies that a detailed model describing the situation as accurately as possible might be indeed quite useful for public health professionals. Such a model might have many equations and in practice may be only solved approximately by numerical simulations. This has become feasible in recent years because of the developments in high-speed computing.

In these notes we concentrate mainly on simple models in order to establish broad principles. These simple models have value as they are the building blocks of models that include more detailed structure. One use is to compare the dynamics of simple and slightly more detailed models to see whether slightly different assumptions can lead to significant differences in qualitative behavior. In the first four lectures we describe general classes of models that should be viewed as templates to use in modeling specific diseases with the incorporation of properties of the disease.

However, it is important to recognize that mathematical models to be used for making policy recommendations tied in to management decisions must be quite different. Models needed for the exploration, development, and implementation of public health policy require the incorporation of a great deal of detail as they must often address scenarios accurately. For example, if the problem is to recommend what age group or groups should be the focus of attention in coping with a disease outbreak, it is essential to use a model that separates the population into a sufficient number of age groups and recognizes the interactions between different age groups. The increased availability of high-speed computing in the last few years has made use of such models possible. The intensive use of agent-based models has also brought to the forefront the use of computationally explicit models in the development of timely and reliable public policy.

Acknowledgments

The preparation of this notes expands and complements the lectures given for the CBMS workshop *Mathematical Epidemiology with Applications* funded by the National Science Foundation and held at East Tennessee State University (ETSU) from July 25–29, 2011

(NSF-CBMS Regional Research Conference in the Mathematical Sciences: Mathematical Epidemiology with Applications, National Science Foundation grant DMS-1040928; Ariel Cintron-Arias (PI); Anant Godbole (co-PI), Principal Lecturers: Carlos Castillo-Chavez and Fred Brauer). There are many individuals that we must thank. The 50+ participants that listened to us for a whole week certainly need to be thanked. Professors Ariel Cintron-Arias and Anant Godbole, who wrote the grant proposal that funded this workshop and carried out the administrative, organizational, intellectual, and social activities that are essential for a successful workshop, deserve a special note of appreciation. Kamal Barley did all schematic and graphic illustrations and helped with the graphic formatting, while Raquel Lopez and Emmanuel Morales provided invaluable assistance with \LaTeX coding. The material presented in this monograph came from our own past research efforts, *some* classical articles, and published manuscripts that we have found useful, inspiring, or noteworthy. We have also made use of existing collections of articles that included one or both of us as editors. The American Mathematical Society (AMS), the American Institute of Mathematical Sciences (AIMS), the Mathematical Biosciences and Engineering (MBE), the Royal Netherlands Academy of Arts and Sciences (AIMS), Springer-Verlag of Heidelberg/Berlin are the journals or publishers that kindly gave us permission to use several of the figures and tables that appear in the text (or modifications). They came from earlier published articles as noted in the text. We thank them. The bulk of Castillo-Chavez's chapters were written while he spent two months in treatment for a (noncommunicable) disease and in residence at the Center for Communicable Disease Dynamics (CCDD) within the Harvard School of Public Health, a center supported by grant U54GM088558 from NIGMS to Marc Lipsitch. CCDD provided a wonderful intellectual environment that included the extraordinary support of Felisa Nobles and Mel Larsen. FB's research is supported in part by NSERC (National Sciences and Engineering Research Council of Canada). CCC's research is also partially supported by grant 1R01GM100471-01 from the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health. Finally, these were not the best of times but also not the worst of times for CCC. He thanks the support of David Harrington, Xiao-Li Meng, Marcello Pagano, and Marc Lipsitch at Harvard; The AstraZeneca Hope Lodge staff and residents; and Joanne Arruda, Kristen Bertone, Alicia Brodeur, Tom Eggleston, Aymen Elfiky, Sandra M. Kelly, and the incomparable Anthony D'Amico at the DFCI in Boston. Finally, the time provided to CCC for the completion of this work was substantially increased through the support of Deans Robert Page and Sander Van Der Leeuw, Provost Elizabeth Capaldi, and President Michael Crow. Finally, the time provided to CCC for the completion of this work was substantially increased through the support of Deans Robert Page and Sander Van Der Leeuw, Provost Elizabeth Capaldi, and President Michael Crow, and late revisions were supported by the Massachusetts Institute of Technology through the Dr. Martin Luther King, Jr., Visiting Professor Program.

Fred Brauer, Vancouver, BC, CA
Carlos Castillo-Chavez, Tempe, AZ, USA
June 25, 2012

Bibliography

- [1] Anderson, R.M., ed. (1982) *Population Dynamics of Infectious Diseases: Theory and Applications*, Chapman and Hall, London, New York.

-
- [2] Anderson, R.M. and R.M. May (1991) *Infectious Diseases of Humans*, Oxford Science Publications, Oxford.
- [3] Brauer, F. and C. Castillo-Chavez (2012) *Mathematical Models in Population Biology and Epidemiology*, Springer-Verlag.
- [4] Brauer, F., P. van den Driessche, and J. Wu, eds. (2008) *Mathematical Epidemiology*, Lecture Notes in Math. **1945**, Springer-Verlag, Berlin, Heidelberg, New York.
- [5] Diekmann, O. and J.A.P. Heesterbeek (2000) *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, John Wiley.
- [6] Dietz, K. (1988) *The first epidemic model: A historical note on P. D. En'ko*, Australian J. Stat. **30**: 56–65.
- [7] Ellner, S., R. Gallant, and J. Theiler (1995) *Detecting nonlinearity and chaos in epidemic data*, in Epidemic Models: Their Structure and Relation to Data, D. Mollison, ed., Cambridge University Press, Cambridge: 229–247.
- [8] Hethcote, H.W. (2000) *The mathematics of infectious diseases*, SIAM Rev. **42**: 599–653.
- [9] Keeling, M.J. and P. Rohani (2008) *Modelling Infectious Diseases in Humans and Animals*, Princeton University Press, Princeton, NJ.
- [10] Ma, Z., Y. Zhou, and J. Wu (2009) *Modelling and Dynamics of Infectious Diseases*, Higher Education Press, Beijing.
- [11] McNeill, W.H. (1976) *Plagues and Peoples*, Doubleday, New York.
- [12] Thieme, H.R. (2003) *Mathematics in Population Biology*, Princeton University Press, Princeton, NJ.