PANDEMICS

WHAT EVERYONE NEEDS TO KNOW

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The deviation of man from the state in which he was originally placed by nature seems to have proved to him a prolific source of diseases.

—Edward Jenner (1749–1823), pioneer of the smallpox vaccine, sometimes called the "father of immunology"

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Though I've spent my whole research career working in the area of infection and immunity and have attended many broad-ranging scientific conferences and served on committees and task forces focused on issues to do with global infectious disease, my specific expertise is neither in public health nor in clinical medicine, both of which are obviously central to this book. I am thus enormously grateful to colleagues who have given their time to critique some or all of these chapters. In this context, I give particular thanks to my infectious disease physician friends, Miguela Caniza, Graham Brown, Ian Gust, and Stephen Kent. Rob Webster and Anne Kelso scrutinized what I wrote about influenza and pandemics in general, while Colin Masters read the chapter on vCJD and mad cow disease. John Mathews provided useful comments on the overall theme. Illustrations have been sourced online from the CDC and the Images Archive at the National Library of Medicine, the WHO Regional Map is reproduced with permission from the WHO, and I thank my close colleague Rob Webster for the other material presented in the figures. I also thank my wife Penny for reading the text, editors Tim Bent and Keely Latcham at Oxford University Press, and my agent Mary Cunnane.

ABBREVIATIONS

AFRIMS	Armed Forces Research Institute for Medical Sciences
AIDS	Acquired immune deficiency syndrome, caused by HIV
B cells	Ig+ lymphocytes that become the antibody producing plasma cells
BCG	Bacillus Calmette Guerin, a TB vaccine strain
BSE	Bovine spongiform encephalopathy; mad cow disease
CCR5	Chemokine receptor 5, one of the two HIV receptor proteins
CCU	The British MRC Common Cold Unit on Salisbury Plain (now closed)
CD4	Surface protein marking "helper" T cells that promote immune responses
CD8	Surface protein on "killer" T cells that destroy virus-infected cells
CDC	The USPHS Centers for Disease Control and Prevention, Atlanta, GA
cDNA	Complementary DNA made from RNA using RT, for the PCR
CJD, vCJD	(variant) Creutzfeldt Jakob disease, a TSE

CMV	cytomegalovirus, or HHV5, a persistent herpesvirus
CO_2	Carbon dioxide
CoV	Coronavirus
COPD	Chronic obstructive pulmonary disease
CTL	Cytotoxic T lymphocyte, the same as a CD8+ killer T cell
DNA	Deoxynucleic acid; the hereditary material of some viruses and all cells
DHF	Dengue hemorrhagic fever
DOT	Direct observed treatment, for those with TB who may be non-compliant
EBV	Epstein Barr virus; causes infectious mononucleosis and some cancers
ECDC	European Centre for Disease Control and Prevention
ECMO	Extracorporeal membrane oxygenation, as in a heart/lung machine
ELISA	Enzyme-linked immunosorbent assay; detects antibodies by color change
FDA	U.S. Food and Drug Administration, which licenses drugs and vaccines
flu ABC	Influenza A, B, and C viruses
FMD	Foot and mouth disease, of cattle
GAVI	The private Global Alliance for Vaccines and Immunization
GI	Gastrointestinal; of the gut
GRID	Gay-related immunodeficiency disease, an early name for AIDS
H	Hemagglutinin protein, the primary target of flu-specific antibodies
HAART	Highly active antiretroviral therapy; multi-drug treatment to control HIV
HepA-E	Different viruses that cause human hepatitis
HHV	Human herpesvirus
HHV6&7	HHVs that cause human roseola infantum

Hi-path	High pathogenicity, or virulent, influenza A virus
HPAI	Hi-path avian influenza A virus
HIV	Human immunodeficiency virus, the cause of AIDS
HSV1&2	Herpes simplex virus variants causing cold sores (1) and genital issues (2)
IFN-	Interferon, a secreted defense molecule involved in virus control
Ig	Immunoglobulin, or antibody that may be of the IgG, IgE, or IgA class
KSHV	Cancer causing (in AIDS) Kaposi's sarcoma herpesvirus (HHV8)
LCMV	Lymphocytic choriomeningitis virus; a mouse virus that infects humans
Lo-path	Low pathogenicity, or mild, influenza A virus
LPAI	Lo-path avian influenza A virus
M2	The matrix 2 ion channel protein that is at low levels on flu viruses
mAb	Monoclonal antibody: Ig of a single specificity, made in hybridoma cells
MDR	Multi-drug-resistant TB, and other bacteria
MHV	Mouse hepatitis virus, a coronavirus
MRC	The British Medical Research Council, equivalent to the U.S. NIH
mRNA	Messenger RNA, the template for making proteins
MSM	Men who have sex with men
N	Neuramininidase, the second (with H) protein on flu viruses
NA	Nucleic acids, the hereditary template of life
NIAID	National Institute of Allergy and Infectious Disease, part of the NIH
NIH	National Institutes of Health, the U.S. funding agency for medical research
NPC	Nasopharyngeal carcinoma caused by EBV, mainly in ethnic Chinese
O_2	Oxygen

OIE	Organization Internationale des Epizootiques, UN agency in Paris
OPV	Oral polio (Sabin) vaccine
PCR	Polymerase chain reaction for expanding viral, and other, NA sequences
PEPFAR	President's Emergency Plan for Aids Relief; supplies drugs to the poor.
PM	Post mortem
Polio	Poliomyelitis, or infantile paralysis, caused by a picornavirus
PrP	Prion protein, the cause of the TSEs including BSE, CJD, and vCJD
PUO	Pyrexia (fever) of unknown origin
RBC	Red blood cell, or erythrocyte that carries O_2 around the body
RHD	Rabbit hemorrhagic disease, caused by a calicivirus
RNA	Ribonucleic acid, the hereditary material on many of the smaller viruses
RRV	Ross River virus, an Australian alphavirus
RT	Reverse transcriptase, a virus enzyme copies RNA back into DNA
SARS	Severe acute respiratory syndrome, caused by a bat CoV
SCC	Squamous cell carcinoma, in the liver of HepB and HepC cases
SiRNA	Small interfering RNA, a molecular regulator
SIV	Simian immunodeficiency virus, causes AIDS in some monkeys
SSPE	Subacute sclerosing panencephalitis, caused by defective measles virus
SW	2009 H1N1 swine flu pandemic virus
T1/2	Half-life, typically of a drug or injected monoclonal antibody in blood
TB	Tuberculosis; lung disease caused by *Mycobacterium tuberculosis*

T cells	Thymus-derived lymphocytes, sets of circulating white blood cells
TDR	Total drug resistant, particularly TB
TSE	Transmissible spongiform encephalopathy, caused by PrPs
TTSH	Tang Tock Seng Public Hospital, Singapore
UN	United Nations
USAMRID	U.S. Army Medical Research Institute for Infectious Disease
USPHS	United States Public Health Service
WBC	White blood cell: moncocytes, neutrophils, T&B lymphocytes, and more
WHO	World Health Organization of the UN
WNV	West Nile virus
XDR	Extreme drug resistant TB, and other bacteria
YFV	Yellow fever virus

INTRODUCTION

Pandemic—we react immediately and viscerally to the word, which seems so close to "panic," though they actually share no etymological connection ("panic" derives from the Greek mythological creature Pan). But pandemics can cause panics, and the sense of imminent danger may be more universally contagious than any virus or bacterium. A lethal virus spreading rapidly and inexorably is, to most of us, a truly terrifying thought, so much so that it pushes other nightmare scenarios that generally hover at the edges of our consciousness (terminal cancer, leukemia, incipient dementia, stroke, quadriplegia, cardiomyopathy, and so on) into deep background. Still, should a pandemic hit, it's essential that we don't go into panic mode. We need to keep our wits about us.

This book is intended to help in that cause. Rather than focusing on the high drama that goes with chasing down dangerous pathogens, the basic intent is to supply accessible information about what's out there and what we should do when a threat emerges. While my personal involvement with infectious diseases is laboratory based, I've had a lot of help from medical friends who deal with the clinical and public health realities. Then, as a research investigator and nonfiction science writer who has increasingly been drawn into various public debates, I'm also very conscious that an acute sense of dread can seize some of my fellow citizens, including many who are well educated, when it comes to understanding the intricacies of disease processes. Some experience a gut-wrenching sense of

revulsion when they encounter technical terms. This book contains a few. But I hope that readers won't simply give up when they come across the first bit of scientific jargon. To understand both infections and what to do about them, we need to know something of the vocabulary that's used by the professionals. I do my very best to explain matters in an accessible way, beginning with a synopsis of infection and immunity, the basis of any discussion of pandemics. And in the hope that you will be persuaded to persist with that little science/technology tutorial, I've also included a few human stories and even the occasional outrageous statement.

We all benefit from understanding at least a little about the various viruses, bacteria, and other bugs that have the capacity to live in and on us. After all, they are in many senses our most intimate associates. When a head cold or mild flu-like illness spreads, we experience a gentler form of what would happen when a genuine pandemic virus comes on the scene. It is my hope that what you encounter in the pages that follow will provide useful background, such that you have enough information to refine your search when you look up your symptoms on the Web, or hold your own when you get involved in a discussion of vaccination, or know what to expect when you travel to regions where dangerous pathogens are circulating. Readers with some background in biology or medicine may feel tempted to skip this brief summary, though I must confess that as I went about the process of checking some of my facts, I realized that there were some points on which my understanding was flawed, and I've been doing research on infection and immunity for 50 years.

A word about medical terms that are in common use but not always understood. I will, for instance, be talking about two "syndromes," as in SARS (severe acute respiratory syndrome) and AIDS (acquired immunodeficiency syndrome). A syndrome is a complex, newly recognized condition about which we know the "what" but not the "why," though the label often sticks after we do work out the "why." A familiar example is Down syndrome, a developmental abnormality

associated with the presence of all, or part of, an additional 21st chromosome. First described in 1866 by the British physician John Langdon Down, it took almost a century to establish the genetic basis of this characteristic condition. Though such names are firmly embedded in clinical practice, modern, evidence-based medicine identifies new diseases by their known cause (etiology) rather than by the name of an eminent doctor or by some symptomatic shorthand. The cause of SARS, for instance, was soon worked out, though not before the disease had achieved broad notoriety. Given the incredible speed of contemporary communication and the short media cycle, the "syndrome" label was firmly fixed in both the public consciousness and the scientific literature.

"Syndrome" therefore reflects that first phase of confusion and, to some degree, fear. When the SARS outbreak seemed to strike out of nowhere in the early years of the twenty-first century, the citizens of Hong Kong and Singapore were terrified. The infection spread extremely fast. People stopped traveling. The effects on local businesses were disastrous (except those selling disinfectants and protective facemasks). The hotels reported immense financial losses. That was also true for airlines. While SARS was essentially dealt with—identified and contained—in the course of six to eight months, the economic consequences were still being felt two years later.

Rational thinking can quickly be compromised by pervasive fear, even when the situation may not be all that bad. I happened to be in Toronto in October 2009 when an otherwise healthy and active teenage boy died of the pandemic H1N1 influenza A virus, known now as the "swine flu." People were deeply shocked and, as the vaccine against this virus was just becoming available, rushed to have their kids immunized. But the logistics of vaccine delivery and the amounts at hand meant that not every child could be protected immediately, a fact that caused general outrage, with parents demanding that the government increase the supply without delay. Yet, six months later, when most had concluded that the "swine flu"

caused a generally mild infection, it was hard to give the vaccine away, even to pregnant women who were, and remain, at significant risk.

As an active member of two research programs (one in Memphis, Tennessee, the other in Melbourne, Australia) that focus on influenza immunity, I was very aware of the efforts being made to sort out the identity of this novel—meaning, as it sounds, previously unknown—version of a familiar pathogen. Both teams contributed significantly to the understanding that some components of the H1N1 "swine flu" virus had been hiding out for more than 90 years in our fellow mammals. The strain that emerged so suddenly in early 2009 was born when two different viruses that infect pigs got mixed up together—a process called "reassortment"—to produce a pathogen that spread rapidly in humans. Looking at the gene sequences of the new virus, scientists soon realized that at least one of the major proteins is very similar to that found by Jeffrey Taubenberger and his colleagues in the "resurrected" genome (completed in 2005) of the virus that caused the 1918 Spanish flu pandemic. While we can't yet reproduce the scenario in Michael Crichton's *Jurassic Park* and bring complex creatures like dinosaurs back from the dead, Taubenberger and colleagues were able to recover virus gene sequences from several different sources of human post-mortem material. These were then "stitched together" to remake the pathogen that caused the Spanish flu, which remains the worst pandemic of modern times. That 1918 "Lazarus" virus is handled under ultra-high-security conditions, for although we know a great deal about these pathogens, there remains much that is not understood about why people die from influenza.

Most of us now associate "pandemics" with "influenza," reflecting the fact that all four acutely lethal pandemics experienced (thus far) in the twentieth and twenty-first centuries (see Figure I.1) have involved the flu. While the very first flu virus was not isolated until 1933, influenza (sometimes known by its French term, *la grippe*) has long been familiar and is

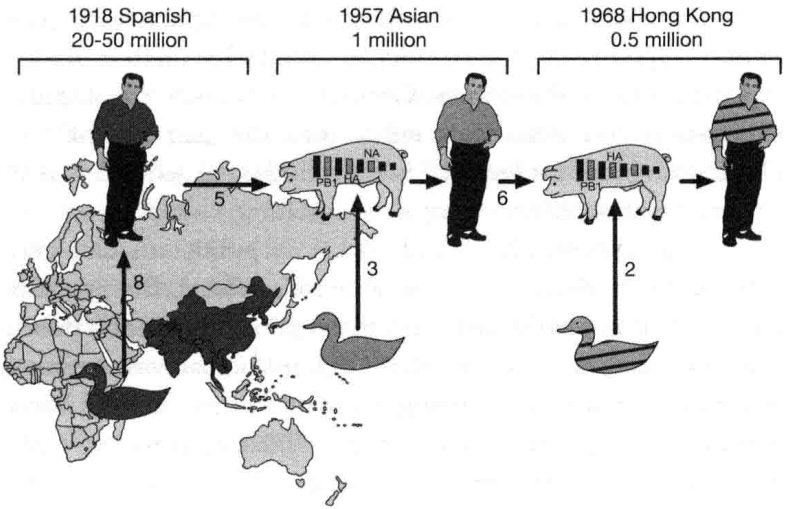

Figure I.1. This summarizes the three influenza A virus pandemics of the twentieth century and illustrates their possible origins, either directly from an avian species (1918), or as a consequence of viruses that are circulating in birds, humans, and/or pigs coming together in the lung of a pig. The small rectangles in the pig symbolize the 8 influenza gene segments that can reassort (mix and match) if a pig lung cell is infected simultaneously with two different viruses to give a novel pathogen that is highly infectious for us, a process called "antigenic shift." The broad virus types are categorized by the numbers assigned to the surface hemagglutinin (H) and neuraminidase (N) proteins present on the outside of the virus particles. The common names given to these viruses reflect where the pandemic was first acknowledged (in 1918) or the virus was initially isolated (1957 and 1968), and the counts below are for those who are thought to have died in the first year or two of virus circulation. Seasonal variants that arise from mutational change ("antigenic drift") in the surface H3 and/or N2 proteins of the Hong Kong flu virus are still circulating in us, with one such strain being the primary cause of the epidemic declared for the United States in January 2013.

Reproduced courtesy of Dr. Robert G. Webster at St. Jude Children's Research Hospital.

clearly described in records dating from the Renaissance and even before. Following the discoveries of Louis Pasteur, Robert Koch, and other nineteenth-century microbiologists, the basic nature of infectious disease was widely understood by the time that European nations and their colonial cousins embarked on that appalling tragedy of 1914–1918, the Great War. According to an account written later by Quartermaster General Erich von Ludendorff, the joint German military commander (with

Field Marshall Paul von Hindenburg), the Spanish flu pandemic helped bring the conflict to an end by further depleting the ranks of the armies. German manpower was rapidly exhausted, and America's entry into the war meant that Hindenburg and Ludendorff were facing what seemed like an endless reserve of fresh troops.

Though initially the Allied and Axis politicians and generals weren't admitting to the disease's effects, the Spanish, who were non-combatants, did the right thing—in the public health sense—and acknowledged that influenza was rampant. Spain gets a bum rap for being open about this. As John Barry describes in *The Great Influenza* (see "Further Reading" list), the virus likely came across to Europe with the newly arriving (from June 1917) American Expeditionary Force. While it was known by the 1930s that the Spanish flu was indeed caused by an influenza A virus, the specific characteristics of this deadly pathogen remained unclear until Taubenberger and his colleagues brought it "back to life" from lung tissue that had been stored for 80-plus years.

The shock of the worst pandemic of modern times was initially blunted by the sheer horror of what had happened in the trenches and battlefields of Belgium and France. In fact, many more were to succumb to influenza than were killed by bombs, bullets, poison gas, diarrhea, bacterial infections like gas gangrene, or simply drowning in the thick mud of Flanders. As described in a contemporary account by physician Victor Vaughan, the bodies of American recruits were "stacked about the morgue like cords of wood," and yet the full extent of the catastrophe was initially concealed for reasons of military security. But the story soon got out and, by the time the Spanish flu hit civilian populations, the fear was palpable. In the end, as many as 50 million people died.

Could the same thing happen today? Modern air travel means that the dissemination of the equivalent of the 1918 virus would be worldwide, perhaps within a matter of weeks. Given that the global population is about four times greater

than it was back then, we could be looking at a mortality rate in excess of 100 to 200 million. That's one scenario. The other is that because of modern medicine the reemergence of a Spanish-like flu virus might not be so lethal. Many who have looked back at the detailed medical and pathology records from that time think that a significant proportion (if not the majority) of the deaths in 1918–1919 were due to the exacerbating effects of bacterial infections that became established on top of the initial, virus-induced lung damage. If such secondary bacterial pneumonia was, indeed, to be a major cause of severe disease in a contemporary influenza pandemic, substantial numbers could be saved by the judicious use of antibiotics, even if the virus spread widely before a vaccine became available.

Perhaps because of the profound trauma associated with the Great War—which obliterated an entire generation of French, German, and British young men (and killed 116, 516 Americans with more than 320,000 casualties)—there is little in the contemporary literature of the 1920s and 1930s that tells of the devastation caused by the flu pandemic. The medical and scientific accounts of the time are written in the dispassionate style of the physician, pathologist, or public health service doctor. As ever, to appreciate the human dimension, we look as much to creative writing as to analytical descriptions by scientists and popular syntheses by nonfiction authors. Katharine Anne Porter's 1939 novella *Pale Horse, Pale Rider* gives us an acute sense of the grief and loss borne by those who survived. More recently, Dennis Lehane's *The Given Day* (2008) interweaves influenza, baseball, Babe Ruth, and the political machinations and corruption affecting the Boston municipal administration and police force. Lehane gives a sense of the courage of the public officials who, though poorly paid, put their lives at risk to help the sick, and describes how some who survived the infection were unable to work again and died young. Published in 2012, Tom Keneally's *The Daughters of Mars* puts a human face to the disastrous loss of nursing staff as influenza compromised all aspects of the war on Europe's