CHAPTER 9

The SARS Case Study: An Alarm Clock?

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9.1 SARS: DEFINITION AND CLINICAL ASPECTS

All animals suffer from infectious diseases stemming from the development of microorganisms belonging to four major categories: parasites, fungi, bacteria, and viruses. In general, it seems that important changes in the ecological niche occupied by an animal result in the development of new diseases [44]. Although most diseases appeared to have coevolved with the branching of animals during evolution – this is illustrated by tuberculosis, caused by *Mycobacterium tuberculosis*, which probably existed well before domestication of cattle [7], some seem to have emerged suddenly. The "Black Death" is an illustrative example. Although it seems difficult to identify its exact origin, phylogenetic analysis has shown that it probably evolved from the much less dangerous *Yersinia pseudotuberculosis* complex, with progressive loss of genes, from the ancient *Y. pestis* subspecies antiqua, to the subspecies medievalis, and the modern subspecies orientalis [1,46]. However, because the reservoir of the agent is large, the disease could only come under control because it was mostly spread through vectors (fleas). In contrast, smallpox (which appeared very long ago, as witnessed by scars present on pharaoh Ramses' V mummy [29]) could be eradicated because there existed an efficient prevention after the experiments of Jenner, and the widespread use of vaccination with a viral strain that had only limited (but real) side effects. Or, rather, we could think it was eradicated [18] until we decided, unwisely, to sequence the genome of the virus. This publicly available data can allow reconstruction of infectious viral particles [17]. In general, we share diseases with warm-blooded animals, and this explains why the practice of butchery seems to be at the origin of unexpected diseases, such as AIDS, now suspected to have arisen from the common use of "bush-meat" [2] in association, of course, with worldwide changes in human behavior. In this broadly outlined context, an outbreak of "atypical pneumonia" affected the Guangdong province of China in the autumn of 2002, and subsequently resulted in a worldwide outbreak under the common denomination of severe acute respiratory syndrome (SARS) [31].

After some controversy (see, e.g., elements of the discussion here [12,23,47]), SARS was identified as a viral respiratory illness in humans associated to a coronavirus [20,34], previously unknown, finally called SARS-associated coronavirus (SARS-CoV). To the best of our knowledge, the illness spread from November 2002 from the Guangdong province to the rest of China and to the world, with a puzzling contagion behavior. Initial rumors about a dangerous atypical pneumonia in the Guangdong region spread through phone SMS from December 2002. One of its noteworthy features was that health workers were often affected. Early in February 2003, the French Consulate in Guangzhou (Canton) closed a high school for fear of contagion. A few days later, the outbreak reached the Hong Kong SAR (China Special Administrative region of Hong Kong). The following months witnessed the extension of the disease to many countries in North and South America, Asia, and Europe, reaching the status of a worldwide epidemic. One of the difficulties of identifying the disease was to find its specific clinical description (pneumonia are frequent in winter time [32]) and to tell it apart from an episode of H5N1 avian flu that affected patients treated in Hong Kong exactly at the same time [41]. Identification of the SARS Co-V followed by the confirmation of the importance of the epidemic. The initial findings were corroborated by other techniques such as immunostaining, indirect immunofluorescence antibody (IFA) assays, and reverse transcriptase-polymerase chain reaction (RT-PCR)

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with sequencing of a segment of the polymerase gene. Other WHO laboratories found similar results.

The etiologic agent responsible for SARS was identified as a novel coronavirus in late March 2003 by researchers in laboratories from Hong Kong, Germany, and many other countries [20,34,43,47], and its genome was rapidly sequenced by a Canadian team [39]. The new coronavirus was isolated in cells from patients with suspected SARS, having direct or indirect links to the SARS outbreak in Hong Kong or Guangdong Province, China, and was identified initially as a coronavirus by electron microscopy (EM) (Fig. 9.1). Despite an unfortunate spirit of intense competition, an initiative from the WHO, the "World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome (SARS) Diagnosis," allowed its members to work together from different research sites through videoconferences and audioconferences and secured Internet web sites. The spread of the epidemic was unconventional, in that different places in the world where contamination occurred had quite different patterns of contagion, morbidity, and mortality. In addition, one observed that children were spared by the adverse effects of the disease. An initial event, traced back to a hotel in Hong Kong, appeared to be the source of most foci in the world, including destinations very far away from one another such as Singapore, Hanoi (Vietnam), and Toronto (Canada) (see Fig. 9.2). The disease spread back from the Guangdong region to Mainland China, Beijing in particular, but not to densely populated regions such as the Shanghai region, despite its intense contacts with Guangdong. Mortality was also very different in different places, with the highest death toll in Hong Kong. This remarkable variability may be due to overreaction of some medical doctors who proposed aggressive treatments in the absence of deep knowledge about the cause of the disease. It could also be due to lack of proper identification of SARS patients, because their status was initially established mostly using clinical and epidemiological criteria only

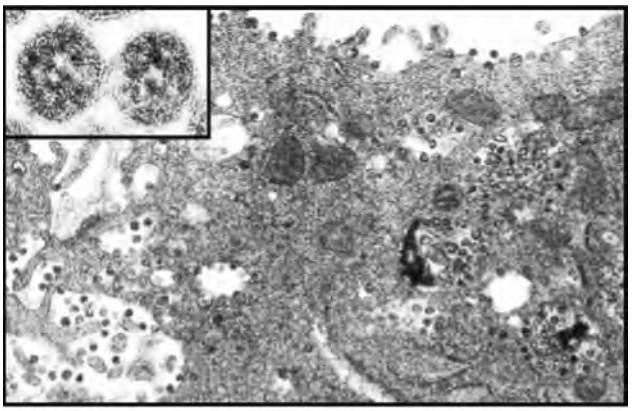


Fig. 9.1. EM of the SARS Co-V (reprinted from [11]).

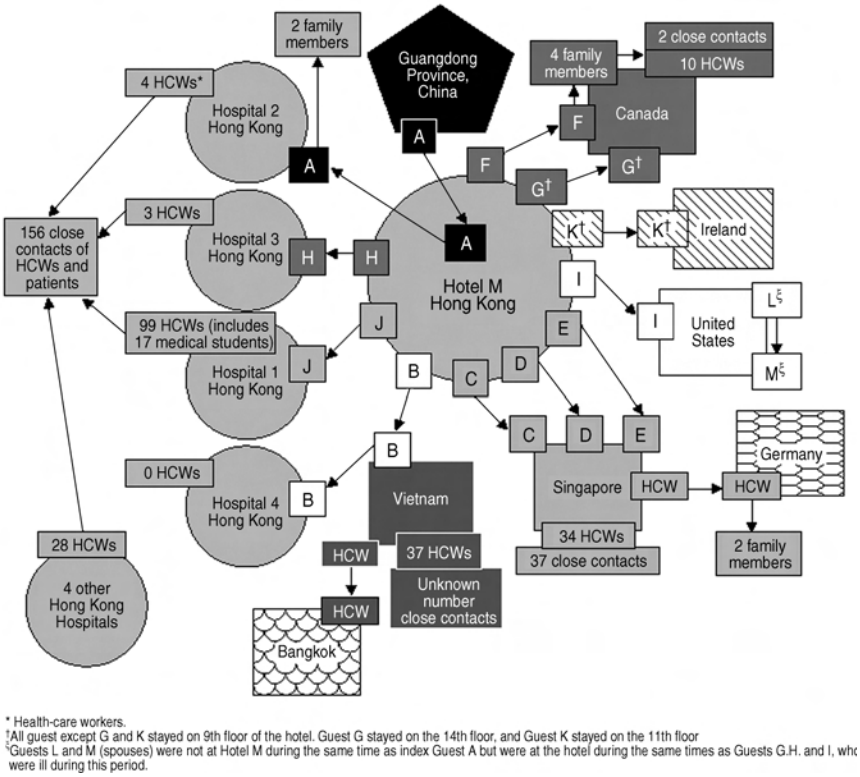


Fig. 9.2. Chain of transmission (reprinted from [11]).

(see [34], supplementary Appendix 1). Retrospective studies indicated that use of the antiviral ribavirin did not improve the condition of patients [37]. A thorough retrospective analysis of the use of steroids is still missing, but anecdotal evidence suggests that continuous supply of steroid might not be optimal [42,59].

Epidemic investigation traced the epidemic evolution back from the patient A. Arrows indicate infection spread either by generating new secondary cases from an index patient or due to the index patient travel. Many of the initially infected cases generated a large number of secondary infections.

Finally, a retrospective study of the sociopolitical context of the time, using information spread through the mass media in addition to that present in fast publication tracks of major scientific journals should be undertaken. It would provide extremely important lessons on the way the world is responding to a highly contagious emerging disease.

The global SARS outbreak of 2003 was finally contained by July 5, 2003, when the WHO reported that the last human chain of transmission of SARS had been broken. Apart from several laboratory accidents causing the re-apparition of the disease (in Singapore and Taiwan in 2003 and in Beijing in 2004), a new SARS episode started late in December 2003 in Guangzhou. Because of the previous experience on SARS, the evolution of the cases, the virus (in molecular terms), and the treatment [62] could be followed in some details. The discovery of the presence of the virus in civet cats enticed some researchers to quickly identify those animals as the source and possible reservoir of the virus [61]. However, several other animals from live animals markets were also found to have been contaminated, and analyses of possible contamination of civet cats in the wild were negative [64]. A retrospective molecular epidemiological study developed by the Guangzhou Center for Disease Control and Prevention, the SARS Consortium of the Minister of Agriculture of the Chinese Central Government and their colleagues showed that the virus genome evolved as fast in civet cats as it did in humans. This was particularly important in that, although civet cats might have contributed to disease transmission, the study strongly suggested that the reservoir is not particularly that animal species [57]. Civet cats, apparently, were contaminated at the same time as humans.

Because they are predators, the obvious inference is that the reservoir is probably a rodent or, with less probability, another small mammal or even a bird. In this respect, the discovery of a highly related virus in Chinese horseshoe bats in Guangdong [35] may be particularly revealing, as bats are not related to rodents (despite their name as "flying mice" or "flying rats" in several languages) but related to Primates, in the superorder Archonta. However, the way the virus might have come into contact with humans is not clear. Bats are used for traditional medicine, and the local population has the habit to eat all kinds of animals. However, among many possible scenarios, they might have been victims of a predator, such as civets (bats are frequently the victims of domestic cats), which might then have passed the virus onto humans. Analysis of the virus genome is consistent with a fast evolution and frequent host shifting [52,65,66] (see Fig. 9.3). This biological background has to be borne in mind when considering the epidemic spread. History of previous coronaviruses epidemics is of particular interest in this context. In the years 1984–1985, an outbreak of respiratory coronaviruses, causing mostly an inapparent infection, spread through the swine population in Europe and then in the United States [36]. Most interestingly, the tropism of the virus had shifted from the gut to the respiratory tract. The change in tropism was the result of a few deletions in the virus genome [50]. Both the parent and the mutant forms later on circulated in porcine herds [33]. This shows that coronaviruses are prone to change in tropism, with concomitant change in virulence. Although truly new emergent diseases can, and will, occur, it is very important to place humans at their place in the phylogeny of animals. In particular, lessons from diseases appearing in domestic animals should be included in the surveillance of human emerging diseases, as they may indicate routes followed by pathogens to spread to animal populations, humans included [58].

We close this introductory part with a brief classification of viruses; we refer the reader to other chapters of this volume for details on phylogeny (contribution by J.R. Stevens and T.A. Richards), unicellular and pluricellular parasites (chapter by F. Thomas et al.), or bacteria classification (contribution by R. Piarroux and D. Bompangue). The metaphor of the "genetic program" is so apt to describe life that, at least at a conceptual level, cells can be described as computers making computers. Within this frame of thought, three "operating systems" would define the three major empires of living organisms, the Archaea, the Bacteria, and the Eukarya. To each of those are associated pieces of program, viruses, that have reproduction as a main goal, in a more or less selfish way. This is why, returning the metaphor, computer sciences speak about "viruses" to describe such pieces of software that propagate through computer networks.

In living organisms, viruses cannot simply be pieces of software, they need to be made of some material, and that material needs to be protected by an outer shell (which can have several names: capsid, envelope, etc.) and designed to recognize a particular target cell. The minimal genetic program of a virus consists of a replication system, and one or usually several proteins involved in the capsid formation (including appendages such as tails, spikes, etc). Because viruses need to interfere with their host cells, their genome often codes for many proteins interfering with the metabolism of the host, diverting it to permit virus development. In some cases, they even code for metabolic enzymes (such as thymidine kinase in herpes viruses [6]) or enzymes or factors of the translation machinery (such as translation initiation factors, aminoacyl-tRNA synthetases or tRNAs [13]). However, they neither code for the core of the translation machinery nor of the core

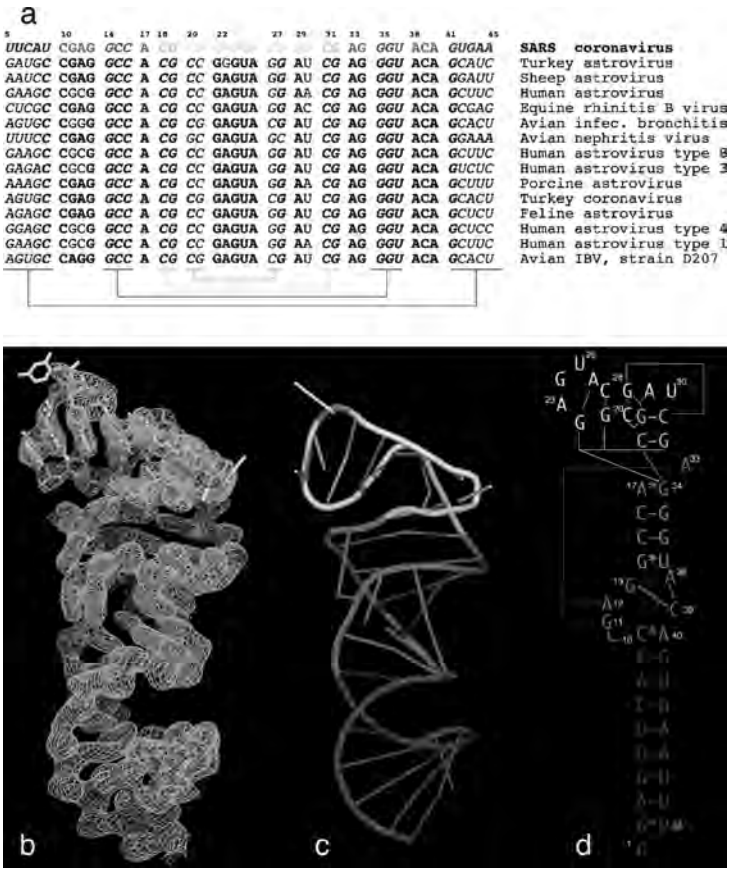


Fig. 9.3. (reprinted from [54]). The primary, secondary, and tertiary structures of the SARS s2m RNA. (A) Phylogenetic comparisons of RNA sequences from various viruses. The SARS RNA sequence is color coded to match the color scheme used throughout. Conserved sequences are highlighted as bold letters, and co-varying sequences involved in conventional RNA helical base pairing are indicated in italics. Sequence complements are indicated using color-coded brackets. (B) Experimental electron density map contour that allowed unambiguous tracing of the RNA molecule. (C) A corresponding ribbon diagram highlighting the unusual fold. (D) Schematic representation of the RNA secondary structure with tertiary structural interactions indicated as long-range contacts. See color plates.

metabolism, making them necessarily parasites, and, as such, not endowed with life. Some viruses can integrate the host genome as proviruses, and stay there until some signal triggers their development. This latter feature is particularly important, as it means that those viruses can lay dormant for a long time (and even throughout generations) and be suddenly reactivated, creating havoc. They can become defective, and unable to reproduce, but this ability can be restored by recombination with an active virus, creating a variety of new variants, or simply by functional complementation. Hence, a remnant of a provirus in a genome can never be considered as completely innocuous. Associated with these properties, the following general classification has been proposed:

- The double-stranded DNA viruses (e.g., Adenoviridae, Herpesviridae).
- The single-stranded DNA viruses (e.g., Parvoviridae).
- The DNA and RNA reverse transcribing viruses (e.g., Hepadnaviridae, Retroviridae).
- The double-stranded RNA viruses (e.g., Reoviridae).
- The negative single-stranded RNA viruses (e.g., Bornaviridae, Filoviridae, Paramyxoviridae).
- The positive single-stranded RNA viruses (e.g., Coronaviridae, Picornaviridae).

In the latter category in particular, viruses can have a segmented genome. This is the case of viruses important for health such as the influenza viruses and the hantaviruses.

Other related agents, such as satellites or viroids are not described here. A universal system for classifying viruses, and a unified taxonomy, has been established by the International Committee on Taxonomy of Viruses (ICTV) since 1966 [30]. The system makes use of a series of ranked taxons, in a classical cladistic way:

- Order (-virales) being the highest currently recognized.
- Family (-viridae).
- Subfamily (-virinae).
- Genus (-virus).
- Species (e.g., SARS coronavirus).

Although the spread of the 2003 SARS outbreak was of less important magnitude than other worldwide epidemics, it has attracted attention due to its special characteristics that suggested the need for tailored approaches both in theoretical modeling and in clinical practice. Interest for the disease was also triggered by the high mortality of the infected patients [19] and its apparent resistance to standard approaches, resulting in worldwide negative economic consequences. However, the overall reaction of the health care and researchers communities in the world was remarkably positive in that the virus was identified only a few weeks after the first cases were discovered. Furthermore, the outbreak was put under control in a few months time. Whether this is due to proper reaction of sanitary authorities or the particular features of the virus and disease remains yet to be explored, both with theoretical epidemiological models and molecular epidemiology studies.

The symptoms of the SARS, that created its name, correspond to a highly virulent disease. Beside patients with a limited contagion pattern, some patients were super spreaders who caused many secondary infections. However, should one consider every SARS-infected individual as a super spreader, the disease would soon have been out of control; fortunately, this is not what happened, as many people seemed to be shielded from infection by some unknown circumstances. Common sense suggests that stricter hygiene conditions would necessarily contribute positively to widespread protection with epidemic propagation being blocked at places with strict sanitary policy. In contrast, if we analyze the reality of the disease propagation, we must note that medical personnel, air travelers, and airport personnel were among the most affected by the disease, whereas other, less specific social environments seemed to go unaffected.[1] The phenomenon is reminiscent of the "herd immunity" concept central to the theoretical simulations of epidemic spread (we will come back to this, with further details, on the mathematical modeling in the next section). At its origin, this concept was used to explain why, during the course of an epidemic, some individuals do not develop the disease even if they are not immunized against it. In such a description, the epidemic results from a balance between the speed of propagation and the responsiveness of the quarantine and other health policy measures, and the number of individuals that are not infected by the disease is determined by these parameters. For the SARS 2002–2003 episode, the propagation of the disease suggested some sort of pre-existing protection, but its cause and explanation still remain to be found. Nevertheless, it was observed that, contrary to expectation, places with lower hygiene seemed protected against SARS, whereas places with more strict sanitary conditions were mostly affected. Furthermore, and this still requires an analysis, children and younger adults did not have signs of the disease.

Before going into specific analysis of the virulence and infectivity of the SARS-CoV, let us point out another circumstance that affects the long-term evolution of the disease. As is the case in the paradigm of ecological biosystems, an equilibrium often tends to govern the relationship of the virus with its host [24–26,51,60]: if the virus is too virulent, then it will prevent further transmission by the host (e.g., because the host dies or is rapidly quarantined). If, in contrast, the virus is less virulent, it will not be able to reproduce itself efficiently. The equilibrium can be either static, where the levels of virus and the host stabilize to some constant values or dynamic when those values evolve in time in (periodic) cycles, as in the simplest predator–prey Lotka–Volterra model. This model describes interactions between two species in an ecosystem, a predator and a prey, and prescribes the equations that model the evolution of the populations of prey and predator [63]. The introduction of an additional species in an ecosystem and its effects have received some attention [16,24]. Note, however, that convergence to a stable or periodic steady state does not appear immediately but needs time to setup; in the meantime, the evolution of the epidemic can be supposed to happen at constant virulence and interaction parameters. For the SARS, it could be argued that a dynamics fitting the standard model was established starting with the second epidemic (2003–2004) because the virus was less virulent; the equilibrium pattern was not apparent in the first 2002–2003 epidemic, so that the standard model cannot explain its dynamics. Other factors have thus to be taken into account.

Let us come back now to the factors that may explain the differences in infectivity under various hygienic conditions. Studies show that the genetic characteristics of the virus have varied [15] during the course of its spreading. This evolution, triggered by the lack of adaptation of the virus to its new human host [57], must have had an impact on its infectivity. It may also have influenced its fitness, as the virus emerged in a localized region and did not yet propagate through different hosts and conditions. From this point of view, the epidemic can be seen as a (averaging) process in which the virus optimizes its characteristics to maximize its chances of

[1] An outbreak of Marburg hemorrhagic fever, caused by a filovirus, affected Angola during the first semester of 2005. Interestingly, as in the case of SARS, the hospital where patients were treated became a source of major contamination. "On 9 Apr 2005, an international medical charity battling the hemorrhagic fever that so far has killed 181 Angolans has urged the government to close the regional hospital here, at the center of the outbreak, saying the medical center itself is a source of the deadly infection. 'Médecins sans Frontières' (MSF), the global relief organization that runs a n isolation ward at the hospital for victims of the deadly Marburg hemorrhagic fever, told Angolan officials on Friday [8 Apr 2005] that the hospital should be closed if the rapidly spreading epidemic was to be contained. Two other hospitals within 60 miles of Uige may also have to be shut down (according to M. de Astellarnau, the organization's emergency coordinator in Uige, the provincial capital where the outbreak was first reported)."

survival in the whole population. However, in the absence of accurate data on the evolution of these precise genetic dynamics, a first approach would be to consider its simplest form where different viruses can be introduced and affect the entire population.

Building on historical data on a set of coronavirus-mediated epidemics that affected pigs in the 1983–1985 [36], Ng et al. [40] introduced the assumption that two simultaneous epidemics interacted. The hypothesis of the *double epidemic model for SARS* that they introduced was based on the high mutation and recombination rates of coronaviruses [28], and on the observation that tissue tropism can change by simple mutations [50] (see Fig. 9.4 for situating the SARS-CoV among other known pathogens).

A Bayesian inference phylogeny of the nucleocapsid protein of coronaviruses, compared with the phylogeny of their hosts (lines drawn between the two phylogenies indicate the host status of each coronavirus), suggests that the SARS-CoV could have resulted both from host-switching and tissue tropism change. This analysis is also consistent with a significant role of recombination [66]. At the time of this analysis, the sequence of Chinese horseshoe bats coronavirus was not known, but we can infer that it would fit extremely well in the picture, as bats are highly related to primates, whereas their coronavirus is highly similar to SARS-CoV [35].

Interaction between both epidemics required involvement of a considerable proportion of the population; accordingly, the first epidemic was supposed to be extremely contagious. As this is often the case with the oro-fecal route, such an epidemic could be propagated by contaminated food, contaminated water, or sewage. It could be caused by some coronavirus, call it virus A. Among its manifestations, examples of visible symptoms would be gastroenteritis (this was consistent with the observed medical data during the winter of 2002–2003 Guangdong and in Hong Kong where many people had diarrhea for about 1 day, but certainly not substantiated by explicit data). This hypothesis is to be related to the above considerations on the optimal balance between the virulence (the facility with which the virus propagates to generate new cases) and aggressiveness with respect to the host (the consequences of the disease in terms of host's health). To ensure its existence even beyond host's death or recovery, an "older," genetically stable virus, would likely display more of the first and less of the second. This perfectly fits with our description. Indeed, it is expected that a virus would rather be moderately pathogenic while retaining the possibility to spread very easily and not the reverse. An additional virus, call it virus B, is responsible for the SARS epidemic. One possible cause for the origin of the virus B is a genetic operator (recombination or more probably mutation [28]) applied to virus A [3,4,22]. Because the virus B is not yet in a stabilized form, its propagation and characteristics

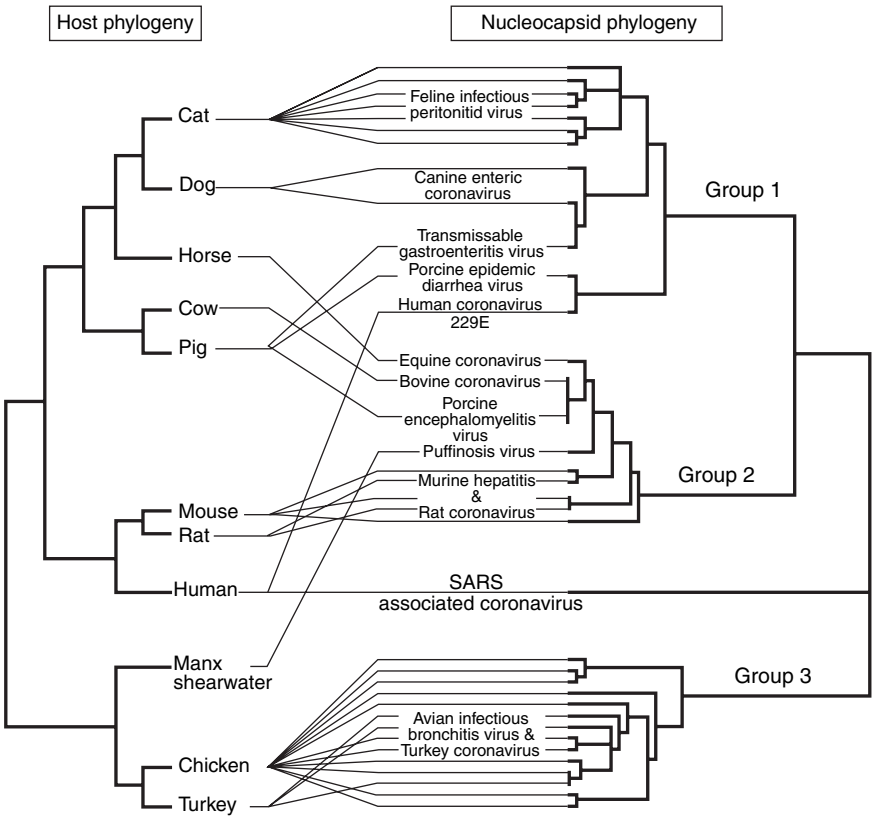
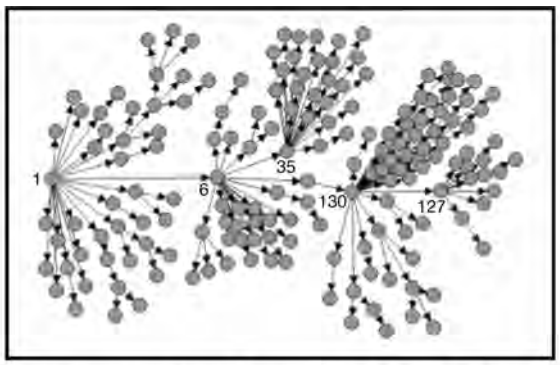


Fig. 9.4. Phylogeny of the nucleocapsid protein of corona-viruses compared with the phylogeny of their hosts (reprinted from [52], copyright (2003), with permission from Elsevier).

are likely to be very different from those of the virus A: virulence should be high to compensate for the small quantity initially produced, but aggressiveness can also be important because it is not yet correlated, through the host dynamics, with virulence. A distinct situation would appear when the viruses have different origin but generate cross-reacting immune responses of the host. In both situations, the epidemics would spread in parallel; because of the common genetic structure or similar host response, it can be expected that the first epidemic would protect against the SARS (so that naïve regions not protected by the virus A can get large SARS outbreaks). These assumptions, which generate a specific spreading pattern of this double epidemic hypothesis, are to be compared to puzzling distribution of the disease evolution in Asia and, for example, the pronounced difference in the status of Shanghai, Beijing, and the mainland. The hypothesis is also to be related with more local characteristics of the spread, as witnessed by the existence of some very infectious individuals but the absence of a worldwide mass epidemic, simultaneously with high infectiveness of health care workers. The environments with less strict hygienic conditions are more likely to be infected with virus A and therefore protected from SARS, whereas in hospitals, the virus A will not gain ground and thus the population will be naïve, thus sensitive to virus B. We will come back to the mathematical description of the model and the fit with the observed results. In a different form, a number of authors speak about "unsuspected SARS patients" [31] that were identified early in the epidemic in Singapore [9] and later in Taiwan [10]. These cases have either atypical symptoms or could not be immediately related to known cases of SARS [38]. These patients may have turned out into reservoirs and affected the latter propagation of SARS. During the course of the epidemic and in the following months, several studies [38,53,56] addressed the structure of the epidemic spread and computed the model parameters that would explain the data. These analyses estimate first the basic reproductive number R_0 that is defined as the expected number of secondary infections generated by an average infectious case in an entirely susceptible population. We propose in Figure 9.5 below a graphical illustration (see also [14]).



* Patient 1 represents Case 1;Patient 6, Case 2; Patient 35; Patient 130, Case 4; and Patient 127, Case 5, Excludes 22 cases with either no or poorly defined direct contacts or who were cases translocated to Singapore and the seven contacts of one of these cases.
Reference: Bogatti SP. Netdraw 1.0 Network Visualization Software. Harvard, Massachusetts: Analytic Technologies, 2002.

Fig. 9.5. Chains of transmission (reprinted from [14]).

When $R_0 > 1$, the epidemic will spread, or otherwise terminate. The parameter was found to be initially above 1 (and thus the disease has the potential to spread to a majority of population), and it then evolved to less than 1 during the course of the epidemic. This change is argued to follow the implementation of the public health policies. Other basic measures that have been investigated are the time from onset of infection to hospital admission or from onset to appearance of clinical symptoms.

9.2 MATHEMATICAL MODELS FOR EPIDEMIC SPREAD PROPAGATION

The mathematical description and modeling of the epidemic spread has been tailored to explain the important characteristics of the disease evolution and its impact on the population. Several descriptions are currently in use depending on the precise practical circumstances, and it is beyond the scope of this chapter to exhaustively address them all. It is nevertheless important to give a brief overview of the methods available to the researcher and on the phenomena that it is possible to transcribe nowadays into mathematical models.

The model that has historically been among the first to capture an important epidemiological phenomenon is the so-called "SIR" model. Its assumptions are fairly simple: the total population is constant in time and can be divided into three classes:

- The "susceptibles," denoted by S, that is, the people that are naïve with regard to the disease (neither had it nor are immune to it).
- The "infectives" denoted by I, those that have been contaminated with the disease. It is supposed that on entering this class, the members can instantly propagate the disease. Also, at the individual level, the disease is considered to begin displaying symptoms and doing its inner work without further delay. We will see later that these assumptions can be relaxed in the "SEIR" model.
- The "Removed" class, denoted by R, contains the people that have had the disease and are either dead or in quarantine, that is, they have been set apart from the entire population and cannot transmit the disease any longer.

Any individual is completely described by specifying the S, I, or R class to which she/he belongs: no further individual differentiation is considered. Every individual in a given class is interchangeable with any other in the same class. The additional ingredient necessary to implement this model is to prescribe how the transition is operated among classes. The overall scheme is the following: from "S" class to "I" class and then to the "R" class: $S \rightarrow I \rightarrow R$. The transition between two classes is governed by the following rules:

- In a given small time interval $[t, t + \mathrm{d}t]$, the transition from "S" to "I" is proportional to the number of S and I encounters (as measured by the product SI) and to the time span "dt." In its simplest mathematical transcription, each of the classes S, I, and R is a time-varying number and its evolution is represented by a simple ordinary equation: $\mathrm{d}S/\mathrm{d}t = -rSI$. If, on the contrary, the evolution is considered stochastically, then the associated stochastic event moves one individual between the classes S and I: $(S, I) \rightarrow (S - 1, I + 1)$. The probability for such an event to appear has an exponential distribution of parameter rI for each member of the class S.
- Besides the incoming dynamics originating from S, the individuals in class I can be affected by their migration to class R. This is supposed to be proportional to the number of individuals in class I, resulting in the evolution equation $\mathrm{d}I/\mathrm{d}t = -bI$, or, at the stochastic level, the event $I \rightarrow I - 1$ is an exponentially distributed random event with parameter b for each individual of the class I. This results in the dynamics of R class to be $\mathrm{d}R/\mathrm{d}t = bI$.

The deterministic variant of the model described above results in the following general form for the evolution of the classes S, I, and R: class S decreases until its final value Sf; class I increases and then decreases; and class R monotonically increases to its final value Rf. The fundamental strength of the SIR model is to capture the so-called "herd immunity": although there is nothing hardcoded into the model to prevent the total initial naïve population $S(0)$ to be infected, it turns out that the final Rf value is less than its maximal possible value, or in other words, S_f is strictly positive. The epidemic extinguishes not because it is short of susceptible individuals, but because, at some point during the epidemic, the infected individuals are removed faster than they are infected. This can be seen from the equation of the classes

$$\mathrm{d}S/\mathrm{d}t = -rSI$$

$$\mathrm{d}I/\mathrm{d}t = (rS - b)I$$

$$\mathrm{d}R/\mathrm{d}t = bI$$

where $\mathrm{d}I/\mathrm{d}t$ decreases (and thus epidemic is extinguishing) as soon as $rS(t) < b$. We recover the basic reproductive number $R_0 = rS(0)/b$, which can be interpreted as the number of secondary infections produced by one primary infection in a whole susceptible population; at a later time "t," the effective reproductive number R_t $rS(t)/b$ can also be introduced. We obtain the fundamental criterion to decide of the state of an epidemic: $R_0 > 1$ means propagation, $R_0 < 1$ means epidemic extinction.

The deterministic model is justified when the epidemic is of large size. In this regime, it can also be regarded as the limit of the stochastic model, which can also be used for smaller sized classes. The meanings of these two models are slightly different: in the deterministic setting, the uncertainties have been averaged out and only the mean dynamics is retained. As such, the simulation is expected to mimic empirically observed figures. On the contrary, in the stochastic setting, each simulation is a possible scenario but all are equally possible. It is crucial to realize that no individual stochastic realization but their averaged trajectory is to be taken as predictor for future evolution of the epidemic. Furthermore, in addition to this average, the stochastic model can also provide the estimate of the deviation from the mean dynamics.

Building on this first SIR epidemic model, it is possible to refine it by including additional classes. An often-used extension is to consider the class of exposed individuals to be placed between S and I. This model applies to diseases with incubation period such as SARS. The flow of individuals between consecutive classes is $S \rightarrow E \rightarrow I \rightarrow R$, and the corresponding equations are as follows

$$\mathrm{d}S/\mathrm{d}t = -rSI$$

$$\mathrm{d}E/\mathrm{d}t = rSI - bE$$

$$\mathrm{d}I/\mathrm{d}t = bE - aI$$

$$\mathrm{d}R/\mathrm{d}t = aI$$

The interpretation of the new parameters is as follows: $1/b$ is the mean time for an individual to stay in the E class, that is, the mean (incubation) time from infection to onset of symptoms (that is supposed simultaneous with infectiousness); $1/a$ is the mean time from onset to hospital admission (or quarantine, or death). These parameters have been estimated for SARS [19], yielding a mean incubation period of 6.4 days (95% CI 5.2–7.7), whereas the mean time from onset of clinical symptoms to admission to hospital varied between 3 and 5 days, with longer times earlier in the epidemic. The same study also provided an estimate mortality rate between 6.8% and 13.2% for patients younger than 60 years and 43.3% and 55.0% for patients aged 60 years or older.

To identify the parameters, the model is fitted to the observed number of hospital admitted cases. These cases are reported per day which, with the above notations, means the values $R(n + 1) - R(n)$ for $n = 1, \ldots$ In mathematical terms, fitting the evolution given by the theoretical model to the observed data is an "inverse problem," which can be recast as an optimization process. This problem may have multiple solutions, and therefore care is to be taken when analyzing the resulting parameters. This is particularly the case for intricate models, which, because of their complexity, will fit virtually any data set (and in particular the actual one) with possibly several solutions for each. Then, the existence of a fit does not by itself necessarily prove that the model is realistic. By contrast, a model that associates a unique solution (possibly with error bars) to a given data set is expected to carry some similarity to the actual dynamics.

The models discussed above stress the importance of the rapid identification and isolation of infected individuals as a mean to control a general epidemic.

Beyond these general theoretical considerations, these models have been used to predict the future course of the epidemics and to asses the impact of the measures taken to contain it. For the SARS 2002–2003 epidemic [38] (see also [21]), data from Singapore and Hong Kong allowed estimation of the reproductive number R by supposing an exponential growth in the number of cases and provided hints of its time evolution. It was found that the epidemic had potential for infecting a large part of the population if not controlled and thus justified the necessity for enforcing stringent health policies. However, due to the presence of super spreaders (individuals who generate many more infections than the average), the estimations of the reproductive numbers still carried large error bars (wide confidence intervals). To further document the efficiency of the health policies, among which quarantine, the same authors introduced subsequently a compartmentalized model similar in spirit to SEIR but with additional classes differentiated over quarantine conditions.

Continuing this analysis, a different approach was taken in [53] that also computed the reproductive number (found as around 2.7 at the beginning of the epidemic if super spreaders are excluded). The paper subsequently evaluated the impact of the public health interventions and argued that the decrease in the reproductive number R was mainly driven by reduction in population contact rates and improved hospital infection control.

Further refined, epidemic specific, health policies can also be assessed if additional spread characteristics are included in the model; these specificities result from collaboration with on-field specialists to allow validation of the hypotheses and make critical use of the highest quality epidemiological data. It is essential for such studies to be made possible during the course of the epidemic. Thus, the data has to be readily available not only to clinicians but also to the scientific community as a whole, in an effort to secure a rapid and timely improvement of the public containment policies.

For the SARS epidemic, additional models are required to explain the long-term persistence of the virus [21] and its spatial transmission differentiation as well as the super-spreader events.

9.3 THE DOUBLE EPIDEMIC MODEL

As an illustration of a model that takes into account the possible existence of a differentiation among the population exposed to the SARS epidemic, we will briefly present below the double epidemic model introduced in [40]. This approach considers that a protective factor exists that can prevent SARS infection even after exposure to the virus. This protective factor is expressed as acquired immunity due to a previous infection with a different coronavirus (or another immunologically cross-reacting virus) that manifests (mildly), for example, as a gastroenteritis that can easily go unnoticed. We will follow the notation of the previous section and design by A the initial mild virus and by B the SARS-CoV. If both viruses have a common structure, it may be possible that individuals infected with the virus A acquire immunity with respect to SARS-CoV. These individuals may either be asymptomatic but propagate the SARS or even completely prevent further SARS propagation. It is the latter hypothesis that we consider here, which results in the decomposition of the total population into subclasses described in the flow chart of Figure 9.6. The class S contains initially the whole population, the $S \longrightarrow E \longrightarrow I \longrightarrow R$ branch models the SARS, whereas the competing branch $S \longrightarrow I_P \longrightarrow R_P$ models the protective epidemic of virus A. This results in the driving equations:

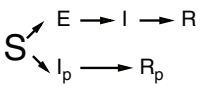


Fig. 9.6. Flow chart of the individuals through mutually disjoint classes in the double epidemic hypothesis.

$$\mathrm{d}S/\mathrm{d}t = -rS(t)I(t) - r_P S(t)I_P(t)$$

$$\mathrm{d}E/\mathrm{d}t = rS(t)I(t) - bE(t)$$

$$\mathrm{d}I/\mathrm{d}t = bE(t) - aI(t)$$

$$\mathrm{d}R/\mathrm{d}t = aI(t)$$

$$\mathrm{d}I_P(t)/\mathrm{d}t = r_P S(t)I_P(t) - a_P I_P(t)$$

$$\mathrm{d}R_P(t)/\mathrm{d}t = a_P I_P(t)$$

Depending on the initial conditions set on the above dynamical model, the protective epidemic can act through two qualitatively distinct scenarios:

- As a "static" protection where initially a large part of the population is immunized (and belongs thus to the class R_P).
- Or as "dynamic" protection where the virus A spreads simultaneously with the SARS: people first infected with A will be protected from SARS, whereas others will remain naïve to it.

This model fitted the data in Hong Kong, Beijing, and Inner Mongolia, and it was seen that both types of protections gave realistic results, with the "dynamic" alternative replicating better the qualitative form of the curves. In all cases, the main epidemiological parameters (basic reproductive numbers, incubation/latent periods, time from onset to hospital admission) were searched for and fit was obtained in ranges compatible with the previous studies.

The fit itself is realized through the optimization of a cost functional F(.) i.e. a function that associates to a given set of parameters the distance between the simulated data (corresponding to the set of parameters) and the actual observed

data (in our case the curve R(t)). This information is fed into an optimization algorithm that finds the set of parameters which minimizes the value of F(·). Because in general there is no analytic formula to operate this inverse mapping, numerical optimization algorithms are used. Standard algorithms include gradient steps [48] or Monte Carlo approaches [55]; additional examples of search procedures use genetic-like algorithms [27] or modified simplex algorithms [5]. It should be noted that often the underlying mathematical optimization problem is difficult, with many suboptimal local optima (imperfect solutions that cannot be improved with local moves), and it is difficult to ensure that convergence to the best possible set of parameters is achieved.

9.4 CONCLUSION

Although the SARS 2003 outbreak was small when compared to other epidemics, its evolution attracted much interest from the public and was followed on a daily basis by people worldwide. During its evolution, the fundamental question was whether the implemented health policy measures successfully worked toward containing the disease. Its special characteristics, namely the presence of super spreaders and the high number of lethal cases among health care workers suggested that much of its evolution was inconsistent and not yet understood at the epidemiological level, whether in its clinical or modeling facets. Combined with the observation of propagation through air travel, such a belief negatively oriented the perception of the potential of the disease to affect a large part of the global population.

Under such circumstances, scientific analyses are crucial, from the very beginning of an epidemic, to provide efficient directions to set up appropriate control measures. As society evolves, the theoretical tools available from classical epidemiological studies have to be adapted to the new socioeconomical conditions. For instance, the costs of containment measures such as quarantine, especially those incurred by the airlines companies, and the losses due to the absence of expected tourism-generated income in affected areas are not negligible and have to be taken into account when designing a control strategy. These socioeconomical parameters may even have a negative impact on data availability, as some local authorities and even governments may be tempted to underreport or declare the epidemic contained too early. To analyze such phenomena, situated at the interface of health policies, economics, and politics, data should be released to scientists at all possible levels. Furthermore, although theoretical methods are likely to exist nowadays to tackle these subjects, meaningful insights and data are often only directed to specialists of a precise discipline (e.g., economic data to economists, health care data to epidemiologists, etc.), preventing a global approach to the situation. As far as possible, an effort is likely necessary from all sides to fill this information gap.

The same comments apply also to the clinical studies. Although national, specialized research institutes remain a necessity, cooperation with foreign teams has proven to be instrumental to rapid advances, for example, to the sequencing of the virus genome, just to cite one. The need for appropriate international collaboration in the field of influenza research, at a time when many fear a new pandemic triggered by the H5N1 virus, is absolutely essential [8]. A complementary point of view would also emphasize that the structural configuration of the clinical research should always allow not only intra-disciplinary mutual enterprises but also inter-disciplinary research with monitoring alternative strategies being a mean to accelerate implementation of meaningful advances. Indeed, epidemiology has a singular standpoint in the field of science because it not only has to deliver verified scientific truths but also deliver them fast enough to be operational for the control of the ongoing epidemic. Splitting the effort into component tasks and listening to all relevant ideas are certainly key to future advances. Of course, once the epidemic is over, the background work that prepares adequate responses to the next epidemic is also crucial. The SARS 2003 epidemic showed that the scientific community can find the tools to react quickly to the demanding tasks raised by an emerging disease. These tools are still perfectible, however, and have to be adapted to address the inevitable future challenges posed by similar epidemics, particularly, flu. It has long been established that flu is a normal, usually innocuous, disease of Anatidae (ducks, geese, and the like). It can spread to other birds, and when this happens, the disease, as expected when the host changes, becomes more virulent initially and then attenuated (this is the normal course of any infectious disease, and this property has been used for the creation of many vaccines [45]). In some cases, the disease can jump to mammals, usually pigs (they are bred, in China, together with ducks in the backyard of farms) and then to humans (remember the Chinese character for "family": a pig under a roof, symbol of the normal happy situation of a farmer). When this happens, we have one of those dangerous episodes witnessed from time to time, and most often coming from Asia, for that very socioeconomical reason. Now, for the present H5N1 strain story, we know (and this is the same for the H7N7 strain [49]) that there was first contamination of poultry (not only Anatidae but also several kinds of fowls: this is why it was advocated in Hong Kong, as early as in 2001, to monitor scavenging birds such as *Milvus migrans*, as sentries for the propagation of the virus), then direct contamination of humans. Because the virus is not adapted to humans, it causes a very extreme reaction, ending, unfortunately, in death. But for that very reason, the virus does not (yet) multiply in humans in such a way that it would cause human-to-human contamination. It is when the virus will have mutated to a less lethal form, it is likely that it will start spreading from humans to humans, and trigger the pandemic many people are afraid of. Whether a "double epidemic" scenario may happen in this case remains to be seen.

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