Working Papers on The Nature of Evidence:
How Well Do 'Facts' Travel?
No. 26/08

The Lives of 'Facts': Understanding Disease Transmission Through the Case of *Haemophilus influenzae* type b Bacteria

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March 2008

"The Nature of Evidence: How Well Do 'Facts' Travel?" is funded by The Leverhulme Trust and the ESRC at the Department of Economic History, London School of Economics.

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The Lives of 'Facts': Understanding disease transmission through the case of *Haemophilus influenzae* type b bacteria

Erika Mattila[1]

Abstract

This article studies how our understanding of disease transmission has evolved over time from the public health perspective. The main question is: What happens to 'facts' in the course of their *life history?* How do they lead their lives? The concept captures the process that shapes the facts of disease transmission, mobilises them via mathematical and graphical representations and allows them to evolve and change over time. So what is actually behind this concept? In my elaboration, the concept of *life history* provides not only analytical but also a metaphorical framework that leads us to follow the development and changes in terms of the phases in life of 'facts': Birth and youth, adulthood and reproductive years, seniority and passing away. Since disease transmission is not a singular 'factual entity', but a bundle of 'facts' binding together knowledge of the disease, its transmission routes, and susceptibility of the population, the particular analytical focus is on how these 'facts' are disseminated via *mathematical*, *graphical* and *model-based* representations. Just as *life histories* are stories full of interactions, surprises and struggles, this article shows the underlying contingencies in the dissemination and accumulation of factual knowledge.

1. Introduction: A life history of 'facts'

Simulations of disease transmission depict multiple aspects of the process: the source or reservoir of the disease, the route of infection (vector), the interaction between the susceptible and the carriers, and the mechanisms of prevention of transmission (vaccinations). In describing this complex sequence, simulation models that produce or circulate this information employ mathematical and graphical representations as a

[1] This research is conducted in a Leverhulme Trust/ESRC funded research project Nature of Evidence: How Well Do 'Facts' Travel? (Grant number F/07004/2) at the Department of Economic History, London School of Economics and Political Science. I wish to thank Professor Mary Morgan for her feedback on this manuscript and my colleagues in the 'Facts' project. Earlier version of this paper was presented in the British Academy Conference: Enquiry, Evidence and Facts. I wish to thank discussions with colleagues in the conference. I am grateful

means to express it in a concise form. Each step embeds multiple 'facts.'[2] Examining the transmission of information between the various communities who have use of it, this paper investigates what effect this process of exchange, transfer, and circulation has had both on the content and the development of such simulations: How did our understanding of disease transmission evolve over time? And what kind of role did these representations play in the process?

These questions can be fruitfully explored through developing as a framework the *life history* of a fact, which invites us to follow the different phases and transitions[3] between them: from birth and youth, through adulthood and the reproductive years, to seniority and passing away. The case in focus is of the transmission of *Haemophilus influenzae* type b bacteria (hereafter Hib) in a population, and the preventive measures taken by public health authorities to avert the life-threatening disease forms the bacteria can cause. The starting point is the moment when epidemiological facts are discovered – *born* – and how the focus on pathogens as singular causes of disease is elaborated towards the population-level concern of disease transmission. The adulthood and reproductive years (to follow our biographical metaphor) will discuss how facts find their independence after being nested in compartmental models: How do our facts *reproduce* themselves in simulation models? The framework of a life history will take us to the detailed Hib

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for the collaboration with researchers at the National Public Health Institute, Helsinki and University of Helsinki, Department of Mathematics and Statistics.

[2] Throughout this paper, the concept of a 'fact' is understood as a knowledge claim accepted within a community and found reliable to be used by them. This 'community' perspective on 'facts' aims to release our thinking from the propositional status of knowledge claims and underline usability and applicability of 'facts'. A similar account is presented by Becker (2007) in which he claims that " […] facts are facts only when they are accepted as such by the people to whom those facts are relevant. [...] [F]acts are not accepted in general or by the world at large, they are accepted or rejected by the particular audiences their proponents present them to" (Becker 2007: 12-13).

[3] The underlying assumption is that life history captures the dynamic, processual nature of life itself. Therefore transitions from one phase to another might not always be simple and smooth, as the psychological literature and its common sense forms notify in terms if *crisis* (e.g. mid-life crises).

transmission models[4] and allow us to observe the maturation of our understanding of disease transmission. Finally, a fact's *seniority* – its old-age and eventual death – is discussed through a process where successful immunisation programmes (predominantly in Western societies) are able to neutralise the threat of severe diseases. Is the 'fact' thus forgotten? Do we neglect the fact that diseases still circulate in those developing countries that have not implemented vaccination programmes?

This study combines historical and sociological[5] perspectives on the life history[6] of facts. In part, it develops Lorraine Daston's notion of analysing the biographies of scientific objects, in which she creates a framework for studying the *vita activa* – the coming into being and passing away of scientific objects (Daston, 2000). It is also close to the notion of *trajectory*, by which Hans-Jörg Rheinberger (2000:273) means that "scientific objects come into existence as a result of unprecendented events [...] and they remain objects of research as long as they have the power to manifest themselves in yet unthought-of ways in the future." Even though this paper is not about scientific *objects* but *facts*, the framework gives insights for the analysis, which (in their terms) aims at reconstructing the *vita activa* of a fact, tracing the "unprecendented events" in which such facts are materialised, described or conceptualised; and following them as they manifest themselves in different ways, and in different contexts or domains of research or research-inspired activities. Yet, *life history* takes a step further than these two notions – *life history* brings forth the different phases, the necessarily processual nature of

[4] This group of models were built in collaboration between University of Helsinki, the National Public Health Institute and Helsinki University of Technology in 1994-2003.
[5] However, this paper does not aim to address the construction processes of 'facts' which has been a central research topic within the micro-sociological studies of laboratory practices (e.g. Latour and Woolgar 1986; Knorr Cetina 1981).
[6] The frame of analysing something in terms of its *life* is successfully applied by e.g. Creager (2002), Mendelsohn (2003). These contributions mainly apply the metaphor of life as a concept that allows observing changes in the object of research (tobacco mosaic virus or cell), however, they do not elaborate the phases of life, as I intend to do with the life-history. For them, the metaphor of life provides a platform to link sequences of change in time together.

living and structures the analysis around the changes in and between these phases. To be more precise: the first phase, birth and youth, documents the emergence of a fact, how its identity is shaped, and tells us about how "knowledge comes into being." The second phase, transition through teenage years to adulthood, shows how the fact is matured, how it appears in flexible ways in mathematical and graphical representations. Reproductive years refer to the third phase, in which general facts of disease transmission are expressed in computer-based models in order to express the particulars of that process. Seniority and passing away is the final phase, at once playing on the idea of the *aging* fact and *forgotten* fact, yet allowing that seniority might also describe an *expert* fact.

The chosen perspective in this paper, the life history of a fact, has shown us that current understanding expressed in scientific facts fluctuates between different scholarly traditions and approaches. Life history not only gives us a vivid framework to look at the different phases of knowledge acquisition and dissemination across time and communities. It also challenges the construction work – what we might call the carpenters' view on scientific work – which has located research activities behind the closed the doors of the construction sites (the laboratories). A life history of a fact thus opens the floor for contingencies, surprises, changes, and forgotten moments.

1.1 On methods and data

This study expands from the core analysis of interdisciplinary model building in infectious disease epidemiology,[7] which is reworked in the section analysing the reproductive years of facts. The expansion reaches towards the history of disease transmission and aligns with "historical

[7] Documented in Mattila 2006a, b and c. The method applied in the PhD project could be assimilated with Latourian empirical philosophy, strongly influenced by micro-sociological approaches in Science and Technology Studies.

epistemology" as presented by Daston (1991: 282): "Not the history of establishment of this or that empirical fact […], but rather history of the competing forms of facticity." Let the observations of the competing "forms of facticity," made in the past and present, form the methodological underpinnings of this study.

The analysis is based on multiple sources of data in order to capture the time dimension necessary for a life span. Historical studies of epidemiology are used as secondary literature to locate the early developments in the understanding of disease transmission and immunity. Epidemiology textbooks document especially the trends in mathematical epidemiology, which introduces us to the general acceptance of modelling methods within the field. A detailed analysis on modelling activities conducted by a Finnish research group is based on a fuller set of data.[8] Scientific publications from the group are the primary source for locating and identifying the facts, whereas analysis of the modelling practices (based on ethnographic observations in the work meetings of the group during 2001-2003) provide insight into the ways in which the general facts from epidemiology and statistics are specified in the model-based representations.

[8] This analysis is based on scientific publications between 1994-2003 and interviews and ethnographic observations in a series of work meetings [n= 22, during 2002-2003 at the National Public Health Institute, Helsinki]. The main idea is to combine both the documentary data with interactional observations in order to show how facts are domesticated in models and what kind of collaborational clarifications, support and argumentation that process requires. The meetings were chosen from the main body of data on the basis of field reports. The selected meetings were then analysed by looking at the topics discussed in each meeting and tracing the talk of transmission. Related topics: carriage, immunity, data acquisition were also located. After the choice and categorisation of the meetings, the transcripts were read and studied carefully, the discussions were linked with other available data from the meetings (versions of models, drafts of articles) and the context of the discussions were analysed by focusing on the 'facts' presented of disease transmission and by the impressions mediated in the discussions – whether a representation or definition of a detail of transmission dynamics was clear to the participants or whether it required further explanations. Also the ways in which the transmission dynamics was 'chopped' in order to be tailored in the model was followed. This was often expressed in terms of searching and defining the optimal parameter values and validating the choice in discussions with epidemiologist. The use of multiple datasets is also a form of triangulation, a process of thickening the description with various sources of data and testing these sources against each other. (Cf. Geertz 2001 on thick description).

This article thus follows the historical development of our understanding of disease transmission – providing a selective historical narrative to the ways in which the singular facts of the microbial mechanisms of diseases were bundled with the facts expressing the dynamics of disease transmission in a population. A key to follow this development are the mathematical, graphical, and model-based representations, which are close to the concept of *mathematization* (in its general dictionary meaning (OED): “mathematical treatment or interpretation; the fact of being treated or expressed mathematically”). My intention is to use the concept to capture the variety of mathematical tools introduced to capture the fine details of transmission facts. The main idea is to see how epidemiological facts are expressed in and through the process of mathematization: how are they simplified, sharpened, circulated, and tailored to disseminate and articulate their knowledge-content in the process.

1.2 Structure of the paper

The structure of the paper follows the phases in a life history: birth, youth, adulthood, seniority, and passing away. These phases provide the framework to trace the way in which understanding of the facts of disease transmission has evolved. Along the way, I will introduce the various mathematical representations that capture the epidemiological facts and offer a backbone to follow the evolution of our understanding of disease transmission through time. The idea is to find a common denominator to the process in which transmission of disease is explored from the public health perspective. Mathematical representations capture the ways in which population dynamics of disease transmission are articulated in mathematical terms, from the early analysis of theoretical epidemiology to our current sophisticated simulation models.

Section 2 explores the birth and youth of disease transmission. It introduces us to the processes of identifying the causative agents of

disease and explores how the public health perspective was brought into the studies. Section 3 analyses how facts of transmission patterns are represented in compartmental models and shows how these facts utilise the models' capacity to simplify the complexity of the patterns into a flexible and spreadable form. Section 4 studies how the facts of disease transmission are reproduced in a simplified, yet informative way in a set of probabilistic transmission models. Section 5 discusses how facts become senior and in what ways they may pass away. Finally, the discussion in section 6 considers why life history is a useful framework to analyse the dissemination of factual knowledge across time and disciplinary communities.

2. Birth and youth of 'facts': From identification of the bacteria to its population level effects

In this section, I will study the discovery and identification of *Haemophilus influenzae* type b bacteria (Hib) on the basis of Koch's, Pfeiffer's, and Pittman's work. I will explore the early phases of the life of Hib, when it was mistakenly understood as the cause of the grave Spanish Flu of 1918. I will discuss how the increase in understanding and detection the particulars of infectious agents was taken to a new level once the mathematical methods of examining the population-level effects and transmission in a population were elaborated. Also taken into account (although only as a side track), is how the experimental epidemiology supported the development of population-level understanding of transmission. This section will conclude with a comprehensive picture of the early phases of Hib studies and public health concerns related to the severe disease forms caused by the pathogen.

Formulation of the germ theory of disease created a new framework to identify singular causal factors behind infectious diseases. Koch's postulates formed the generalised principles for the conditions upon which an organism can be accepted as a cause of a particular

disease. However, the challenge remained how to address disease transmission in a population. For mathematical epidemiologists, the quest was to locate the "global patterns of disease in time, space and population" (Fine 1979). This search resulted in understanding the cyclic patterns of infections (e.g. Hamer 1906), refining the mathematical theory of epidemics that presented the problem of which factors govern the "spread of contagious epidemics" (Kermack and McKendrick 1927), and in an unfortunate conception of *infectiousness* (by Brownlee in Fine 1979).

2.1 Understanding germs, identifying Hib

Our main character, *Haemophilus influenza type* b bacteria (Hib) was first identified as Pfeiffer's bacillus in 1892 by Robert Pfeiffer, who worked with Robert Koch. This was the time of upheaval for the *germ theory* of disease, which was able to establish microbes as causative agents of diseases. The architects of germ theory, Louis Pasteur (1822-1895), Robert Koch (1843-1910), and Robert Pfeiffer (1858-1945), were able to formulate the logical conditions needed to show that some organism *x* is the cause of a disease *y* (Bynum 2006: 123). These conditions are known as Koch's postulates and they can be formulated in the following way:

- The organism must be shown to be constantly present in characteristic form and arrangement in the diseased tissue
- The organism, which, from its behaviour appears to be responsible for the disease, must be isolated and grown in pure culture
- The pure culture must be shown to induce the disease experimentally

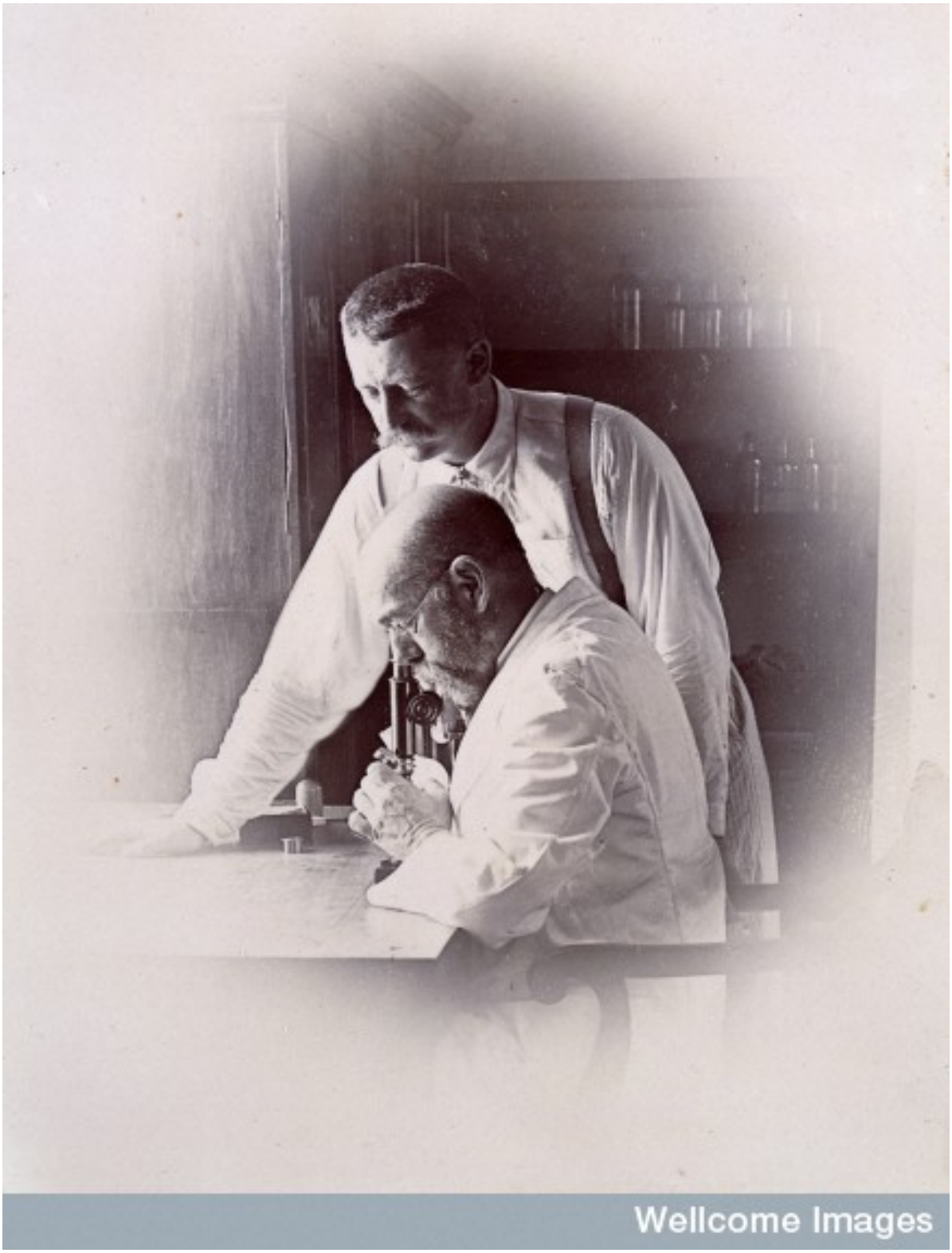

Figure 1: Koch and Pfeiffer working together in India on plague.
(Wellcome Trust Medical Library)

Of course, the idea that microorganisms were a cause of disease had been presented long before the germ theory's[9] iconic formulation through Koch's postulates, though in an unsystematic fashion.[10] The crucial findings of the pioneers of germ theory enabled them to establish as a fact that diseases are caused by microorganisms. This had important implications for the epidemiological study. Firstly, it paved the way to vaccine development and understanding of immunity. Secondly, it made possible the specification of the concepts describing the transmission dynamics. Koch suggested the existence of "asymptomatic carriers," and identified just such a candidate in the well-known case of "Typhoid Mary,"[11] an apparently healthy individual who nonetheless serially infected families for whom she cooked in New York (Bynum 2006, 131). Understanding transmission dynamics also led to studies that aimed at controlling and preventing disease transmission. Experimental epidemiology emerged as a platform[12] for further investigation, expanding the focus towards the understanding of population dynamics of disease transmission[13].

Transmission is an enigmatic feature of utmost importance within infectious disease studies. It has puzzled historians of medicine, especially in the early days when the distinction between infection and

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[9] There are, of course different interpretations of the importance of germ theory, whether it is a unified theory or set of theories led by the practices of identifying the germs (e.g. Worboys 2000). Mendelsohn's analysis (2002) of the 'golden age' in the science of bacteria discusses the differences in major research traditions that lead to the formulation of germ theory.

[10] For example, in the 16th century, Girolamo Fracastoro (1478-1553) said that seed-like entities were capable of transmitting infection by direct or indirect contact. His ideas were close to those of a Dutchman Anton van Leuwenhoek (1632-1723), whose ability to identify micro-organisms through a newly developed instrument, the microscope, offered the early attempts to explain the cause of a disease. However, these ideas were forgotten, and the dominant view, known as *miasma theory* favoured the account that diseases were caused by 'bad air' or poisonous vapours. This account was seriously challenged by John Snow in the mid-19th century, when he traced the source of cholera outbreak in London and showed on a basis of statistical analysis that it was actually caused by contaminated water taken from one specific water pump, and by removing the pump handle, he managed to protect the public from the outbreak.

[11] Mendelsohn (1995) analysed the different notions of *social* in the case of "Typhoid Mary".

[12] The concept of platform is informed by Keating's and Cambrosio's (2000, 2003) analysis of a biomedical platform, which according to their characterisation is a "combination of techniques, reagents, skills, constituent entities [...]".

[13] Cf. Amsterdamska on standardizing epidemics (2001).

heredity was not understood (Gaudillère and Lövy 2001). In a simple classification of objects and patterns of transmission, *horizontal* is linked with infectious agents and *vertical* is seen as transmission of hereditary traits. But the story of infectious transmission is not that simple. Different infections are transmitted differently. Some are constantly present in a population (such as malaria), some occur in serious outbreaks but wane over time (such as cholera). The means of transmission may vary: some pathogens need physical contact, some are transmitted airborne. And it may still not be possible to specify a carrier, a susceptible, or an infected person, for (as with Typhoid Mary) some infectious agents may not always cause symptoms in their hosts. Although brief, this sketched history does underline that transmission as an epidemiological 'fact' is a stubborn piece of knowledge that has required thorough investigations in order to be domesticated.

2.2 From false identity to "blood-loving" bacteria

Even though Pfeiffer succeeded in isolating and identifying his bacillus, it seemed not to be clear which diseases it caused. During the dreadful year of Spanish Flu, some studies identified Pfeiffer's bacillus to be the cause of the disease. Studying the link between Pfeiffer's bacillus and the pandemic influenza, Martha Wollstein argued that:

> There is, at present, hardly any difference of opinion that, with an adequate bacteriological technique, Pfeiffer's bacillus is found to be very commonly present in the respiratory tract of persons suffering from influenza and its attendant pneumonia. (Wollstein 1919: 555)

In her conclusions, she underlines that the strains she was able to isolate during the epidemic were "morphologically and biologically similar to the strains isolated from influenza cases." However, she goes on to add that the "serological reactions are not stable enough" to "signify that Pfeiffer's bacillus is the specific inciting agent of epidemic influenza."

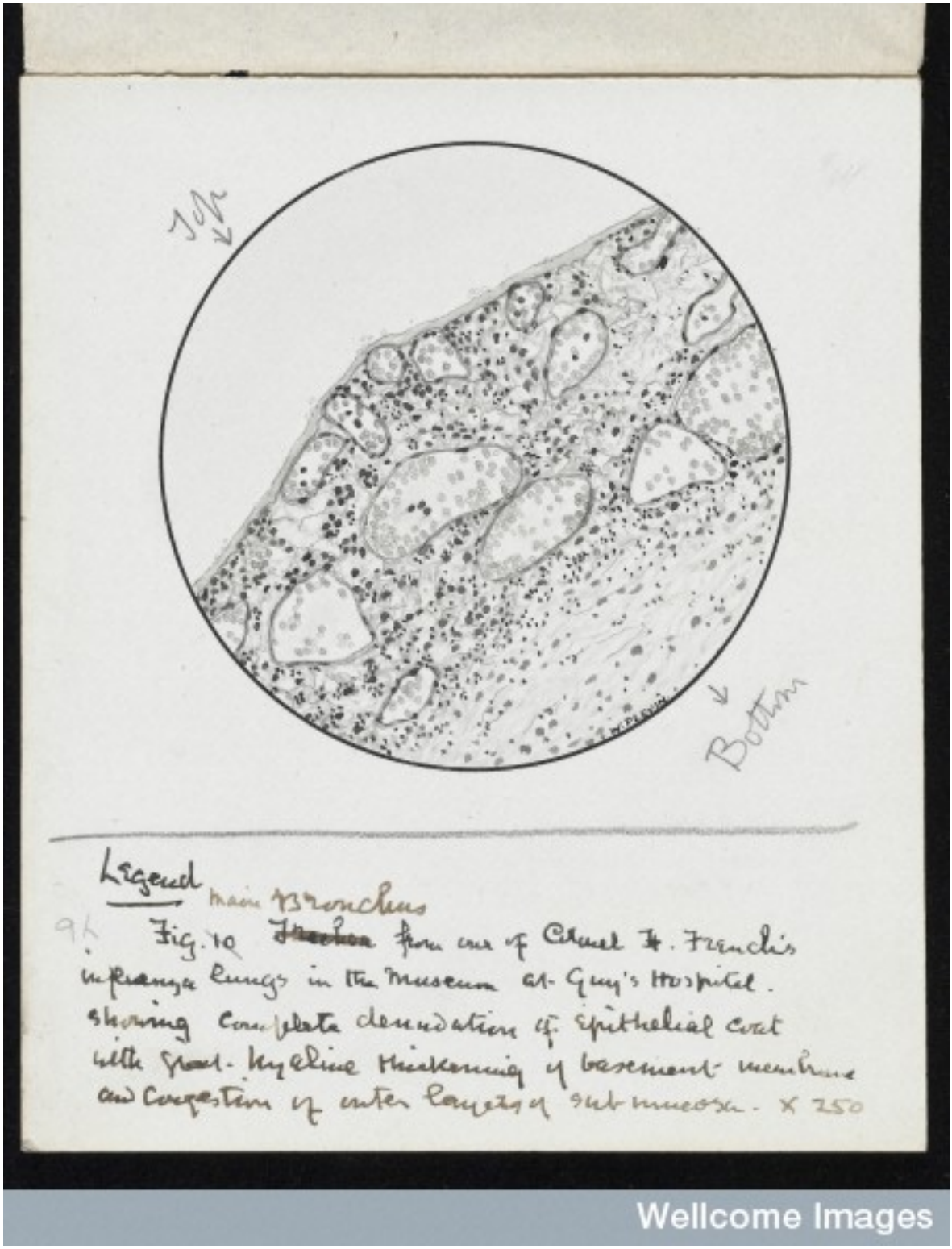

Figure 2: The causative agent of the pandemic influenza of 1918. (Wellcome Trust Medical Library)

In the 1930s, Margaret Pittman, working at the Rockefeller Institute for Medical Research, was able to define two major groups of Hib. Prior to her pioneering work, in the 1920s Winslow had renamed the bacteria “blood-loving” (hence *Haemo*[=blood] *philus*[=loving]) because of the requirement for blood factors for growth. Pittman’s work was groundbreaking: she was able to characterise the distinct strains (*a-f*) that differ in the composition of their polysaccharide capsules (Ward & Cochi 1988).

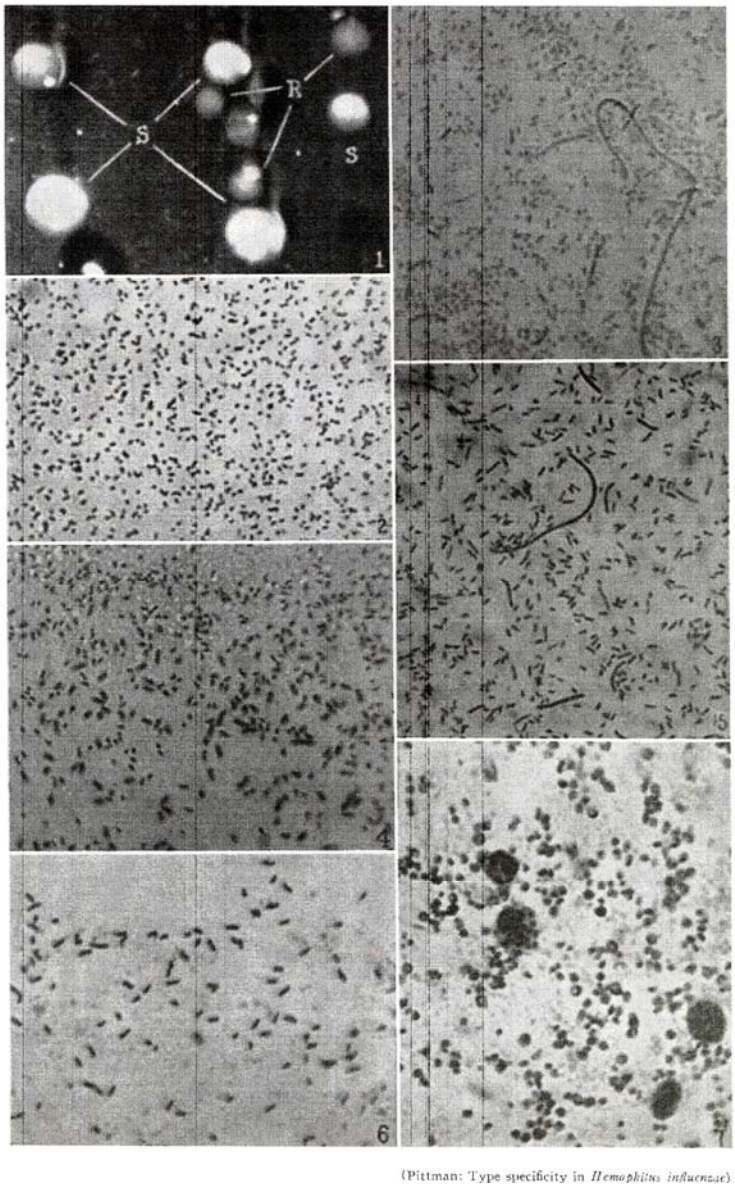

Figure 3: Pittman’s plates to cultivate and characterise the distinct strains of *H. influenzae*. (Pittman 1931)

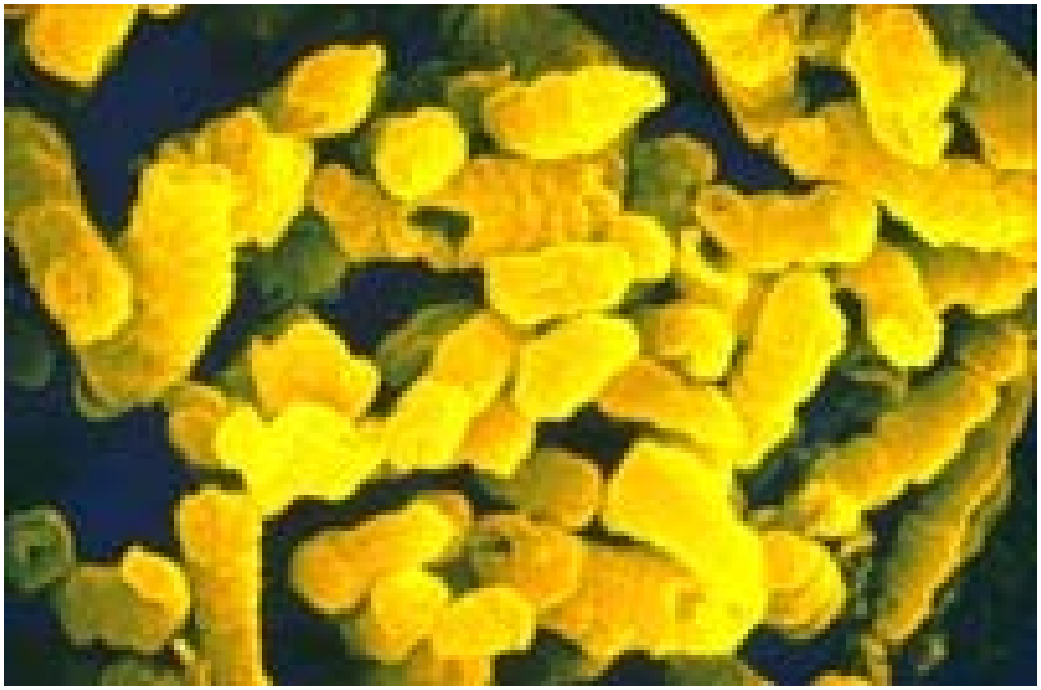

Figure 4: Electron-microscope image if *Haemophilus influenzae type b* bacteria. (www.sanofipasteur.com/sanofi-pasteur/index.js)

Pittman's work[14] paved the way to vaccine development. This is the entry point to our major interest, transmission of Hib. Once the strains were defined, the bacteria were soon identified as a causal of meningitis, a potentially fatal inflammation of brain tissue. Furthermore, the bacteria were observed to circulate among young children, which increased the urge to provide protective measures against the disease. However, it was only in the 1970s that polysaccharide vaccines were introduced, and, to improve their efficacy, conjugate vaccines came on market in the late 1980s. The vaccine development era is also an important moment for Finnish public health. Professor Emerita Pirjo Mäkelä[15] (National Public Health Institute) participated actively in the development work of both polysaccharide and conjugate vaccines. Population-wide vaccinations against Hib began in the USA in 1985, in Finland in 1986, and in the UK in 1992.

[14] Cf. Pittman (1931, 1933)
[15] She enjoyed a significant career as a microbiologist and epidemiologist and she also supported and participated actively to the Hib modelling studies to be discussed later in this paper. She was nominated as the first women to become a Fellow of the Finnish Academy (which is the highest academic nomination in Finland).

Figure 5: Dr Pirjo Mäkelä was awarded the Robert Koch prize in 1970. (Women of Learning online exhibition. http://www.helsinki.fi/akka-info/tiedenaiset/makela.html)

2.3 Towards mathematical representations of disease transmission

As the understanding of the causative agents of diseases evolved, part of the epidemiological and microbiological research followed in the footsteps of John Snow. This meant that the observations of transmission dynamics at population-level became significant. Furthermore, an understanding of the transmission dynamics led to the "removals of pump handles," to the vaccination development and planning of mass vaccination campaigns. But what is the machinery to produce these observations? Populations do not queue for the local surgeries to complain about their symptoms. The public health perspective needed the development of two lines of research. Experimental epidemiology[16] was interested in transmission in populations and through the use of animal experiments, developed

[16] See Löwy (1992) on Haffkine's work on developing anticholera vaccine.

models to observe this. Interestingly, the papers considered these as "artificial epidemics," like H. Amoss's work (1922) on "Artificially induced epidemic of mouse typhoid." With his studies, Amoss was able to present the death rate and bacillus carriage rate related to the phenomena (in this case, typhoid). In the same way, Lurie studied the experimental epidemiology of tuberculosis on guinea pigs (1930). But experimental epidemiology never fully brought epidemiology into laboratory. As Olga Amsterdamska emphasises, "in addition to the microscopes, petri dishes, and laboratory animals, epidemiologists continued using morbidity and mortality statistics, surveys, and historical reconstructions of disease patterns to study correlations among factors involved in the spread and mode of transmission of infectious diseases, the waxing and waning of epidemics" (Amsterdamska 2001: 136). What, then, were these "reconstructions of disease patterns"?

If we follow in the footsteps of Daley and Gani (1999), the history of quantitative studies on human diseases and deaths can be traced back to John Graunt's 1662 work, *Natural and Political Observations made upon the Bills of Mortality*. Following that, a century later, Daniel Bernoulli demonstrated how *variolation*[17] could reduce death rate; and in the 1840s, William Farr studied the progress of epidemics and characterised data from smallpox deaths mathematically. According to Daley and Gani, these were limited approaches, since the understanding of the mechanisms that spread the disease were yet to be discovered.

Once the explorations towards understanding the cause of disease were successful, providing the mindset that allowed the expression of the transmission dynamics in terms of spreading *germs*, the mathematical theory of epidemics started to emerge. Pioneering work by Hamer (1906) elaborated the mass-action principle in a deterministic model of measles outbreaks. His work, "Epidemic disease in England – the Evidence of Variability and of Persistency Type," studies the observations from a

London measles wave and he is able to identify factors affecting the population-level transmission: “alterations of its age constitution, varying customs, and social conditions” (1906: 735). As Soper (1929: 34) emphasises: “Perhaps no events of human experience interest us so continuously, from generation to generation, as those which are, or seem to be periodic.” It is exactly this periodicity that led pioneers in the *mathematization* of epidemiology to observe the patterns of transmission and formulate the early models on them. For example, Kermack and McKendrick (1927) identified the categories of susceptibles, infected, and immunes as players in the typical epidemic. And prior to them, Ross (1911) had observed the periodicity in his studies on malaria. What were then the main contributions of these mathematical expressions?

For the purposes of our story, we may pick up some key expressions following Paul Fine’s (1993: 268) work on the history, theory and practice of *herd immunity*, we learn that the mass-action principle was used by Hamer (1906), and initially formulated on the basis of physical chemical principle that says “the rate or velocity of a chemical reaction is a function of the product of the initial concentrations of reagents.” The law of mass-action captured the relation between susceptibles, infected, and immunes in successive time intervals in simple discrete time mass-action (or Reed-Frost) models. This means that the model expresses the changes in the number of susceptibles (infecteds and immunes) as successive time steps, to be recalculated for each new time period. The phenomenon described by the law of mass-action is re-conceptualised as *herd immunity*. According to Fine (1993), the concept was published in 1923 by Topley and Wilson, who had studied infectious epidemics in laboratory mice. They argued that “the question of immunity as an attribute of herd should be studied as a separate problem” (Wilson in Fine 1993: 266). However, the impact of immune individuals and the idea that they could

[17] Inoculation of smallpox virus from diseased person to a healthy person.

provide indirect protection to others was recognised by Farr in the 19th Century, when he studied smallpox epidemics (Fine 1993: 266).

The theory of herd immunity claims that when diseases are passed from person-to-person, it is more difficult to maintain the chain of infection when large numbers of population are immune. This can be calculated as a *herd immunity threshold*, which is the point at which the vaccinated percentage of a population is such that it effectively stops the spread of the infection, because there is no longer a sufficient number of susceptibles to contract the disease. To calculate this threshold, one needs to define the basic reproductive number, R_0, which is defined as the average number of individuals directly infected by an infectious person during the entire infectious period, assuming entry into a totally susceptible population. In infections that are transmitted from person-to-person, the potential of the spread is called the *reproductive rate*, and depends on the risk of transmission per contact, and on how frequent those contacts are. The reproductive rate is determined by:

- the probability of transmission in a contact between an infected individual and a susceptible one
- the frequency of contacts in the population
- how long an infected person is infectious
- the proportion of the population that is already immune

Thus specified, all these characteristics can be expressed in mathematical equations to provide numerical estimates of the transmission dynamics in a population (Giesecke 2002).

Herd immunity as a fact opened the horizon to observations on how disease transmission is related to population dynamics. However, for public health purposes, the identification of transmission routes was an equally important task. In Snow's London cholera outbreak, the source of the outbreak was contaminated water. Wade Hampton Frost (1927 in Maxcy 1941: 508) describes the "vehicles and conditions of transmission," the process in which "the microorganism escapes from its

reservoir, its portals of entry for establishment in a new host and the conditions necessary for its conveyance from an existing source to this portal of entry." He continues by explicating the "common avenues of escape" for a pathogen – for example, by using the immune-system's purgative reactions as a means of spreading itself through vomiting, diarrhoea, coughing and sneezing; or using the agency of blood-sucking insects. These "common avenues of escape" are later linked with the characteristics and habits of population, and reactions between the microorganism and man, which provide entry points to public health measures.

Currently, transmission routes are listed for person-to-person, air-borne, water-borne, food-borne, and vector-borne infections. In the case of Hib, the transmission route is person-to-person via human excretions from the respiratory tract. However, Hib does not necessarily cause disease, the infected person may remain an asymptomatic carrier, capable of transmitting the bacteria but remaining healthy. This complicated the ways in which Hib transmission was represented in dynamic transmission models, (facts for the specific disease) as we will learn in section 4. Furthermore, Hib vaccine development as a means to prevent the transmission proceeded in two phases. The earlier polysaccharide vaccines were capable of protecting from the disease, but they did not diminish the carriage of the microorganism. Later, the conjugate vaccines did both, which of course affected the estimates of the basic reproductive rate and optimal herd-immunity threshold. Hib is therefore a good case for explaining how the particular epidemiology of a microorganism may actually present challenges to the mathematization of its spread.

How do our facts of disease transmission lead their lives in the early moments of birth and youth? Let us summarise our findings in a following table:

Table 1: Birth and youth of facts.

Phase in life history and its description	**How do 'facts' lead their lives?**	**Representations of facts**
Birth and youth: The phase documents the emergence of the 'fact', shapes its identity, tells us how the 'knowledge comes into being.	Germ theory of disease gives an explanation of the singular causes of disease; public health concern is the transmission and circulation in a population. Identification of Hib, false identity and mixing Hib with influenza virus (causing Spanish Flu).	Early development of mathematical epidemiology (or theoretical epidemiology, Hamer 1906, Kermack & MacKendrick 1927, Soper 1929).

So, this phase was described by the emergence of facts and the shaping of their identity. We may say in summary that facts of disease transmission led their lives in the mathematical expressions developed by early mathematical epidemiologists. Yet we noticed that the identity of the facts was not firm – that there were, for example, competing interpretations of the particular cause of Spanish Flu of 1918. So we may ask, following Latour:[18] "where were the facts of disease transmission patterns before they were identified and represented mathematically?" Our answer reveals the heterogeneity of factual ingredients brought together in terms of Koch's postulates, microbiological findings on Hib, notification of transmission routes, impact of herd immunity (to name only a few). The gradually building understanding of disease transmission faces the fruitful tension between the individual and the population, already in its infancy. For Hamer (1906), it was not enough to explain *singular* causes of diseases, but to find the facts to explain why transmission patterns circulate between populations. In other words, this tension between individual and population begins to build: Tension that

results from the complexity of transmission dynamics reaches from the individuals' states as carriers and infected, to the population-level observations of indirect protection. To increase the understanding of transmission, this tension is mitigated with compartmental representations of the population-level dynamics, which are discussed in the following section.

3. Transition to adulthood: representing facts of transmission in compartmental models

How do facts about transmission come to be represented in compartmental models, and how do these representations facilitate our understanding of the general patterns of transmission? The transition to *adulthood* in our life history is elaborated by following the refinement of previously discussed theoretical and experimental observations of disease transmission and exploring how they become simplified and sharpened into probabilistic infectious disease models. A special focus is on the disease patterns which classify individuals into groups of susceptible, infected, and recovered (or different variants of these). The pathogen-specific transmission patterns are usually expressed as S-I-S, S-I-R or S-E-I-R (susceptible, infectious, infected, and recovered) depending on the bacterial agent in question. They can be represented in *compartmental models*, which divide the population into compartments, i.e. blocks of susceptible, infected and recovered individuals and express in mathematical terms the transitions between these blocks (e.g. the proportion of susceptibles that turn into infected at rate λ). In our story, the pattern is S-I-S (since Hib does not convert to permanent immunity – individuals are S[usceptible], I[nfected], and then S[usceptible] again). These patterns form a generalised body of knowledge that facilitates the parameterisation of infectious disease models. However, in the early phases of epidemiological modelling, this classification led to

[18] Latour (2000: 247) asks: Did Pharaoh Ramses II die of tuberculosis?

deterministic compartmental models of disease transmission. These models are insensitive to the impact of chance in small populations and oftentimes ignore agent-based dynamics. So, this phase of the exploration – the transition from teenage years to adulthood – will clarify the difference between deterministic and probabilistic models, and expand upon the ways of understanding facts of disease transmission in a population.

3.1 Compartmental models: a youth club for teenagers

Let us open our metaphor of life histories a little. After birth and youth, our facts could be seen as teenagers and young adults who are struggling for independence, and searching for their own paths through life. We might accordingly think that the facts of transmission (identified in and emerging from bacteriology, experimental epidemiology, and population studies) begin to search for more independence, their own identity, and paths towards adulthood in compartmental models. What is meant by this? In the earlier phase, the facts were bound up with the experimental setting in which they emerged. However, in this new phase, compartmental models can serve as a *transitional space* between childhood and adulthood. Here, facts are acknowledged as (somewhat) independent pieces of knowledge (about the carrier state, the susceptibility, etc), but yet they are still bound up with the deterministic relations between the different compartments.

What are compartmental models? In simplistic terms, they are models that consider groups of individuals in a population as compartments. By naming these compartments according to the state of infectiousness (of the compartment), one is able to divide the population under scrutiny into smaller units and express (with differential equations) the transitions in relation to the time elapsed between these units. Diagrammatically, movement between compartments is usually expressed by arrows indicating changes in the daily rates (Hurst &

Murphy 1996:5). The usual compartments are *susceptible*, *infectious* and *immune*. These basic categories can be extended to *infected* (but not yet *infectious*), *removed*, or *deceased* – and yet another category can be added to describe those who are protected by maternal antibodies (*immune*, but not due to disease). In addition to these categories, compartmental models describe the interrelations: the transitions from *susceptible* to *infected* to *immune*. The rates of these transitions can then be diverted by interventions: adding vaccinations into the model increases the number of *immune* in the population, for example. The following two figures (from Hurst and Murphy 1996) illustrate the basics of compartmental models:

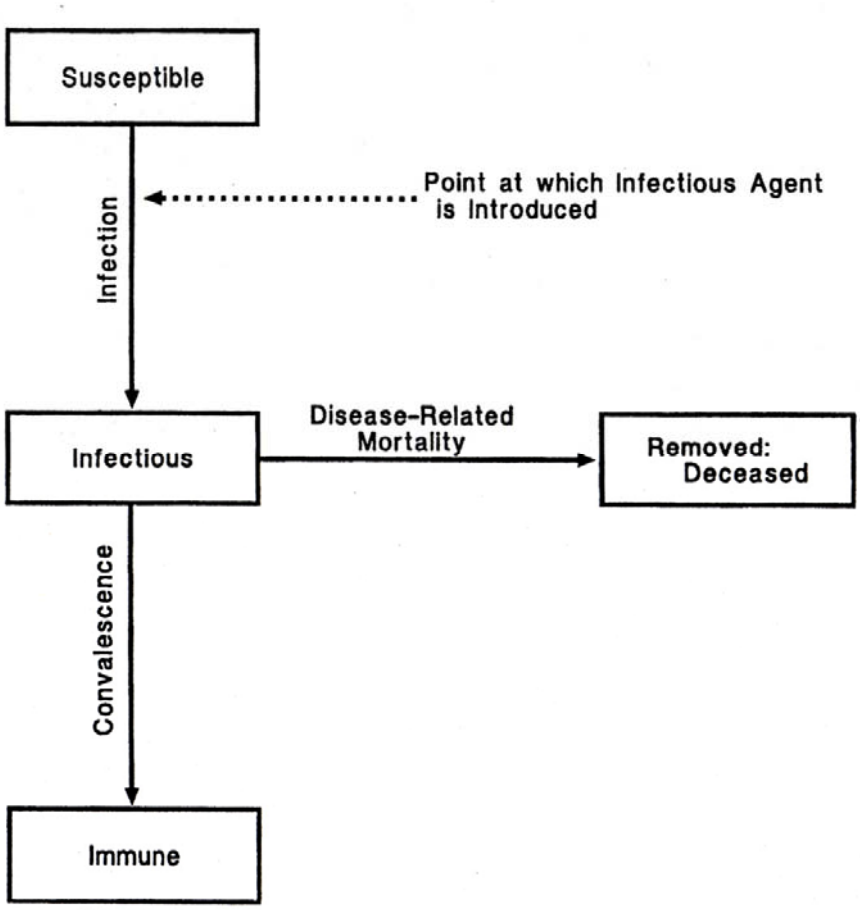

Figure 6: Simple compartmental model illustrating transmission dynamics of an epidemic. This model also shows the point at which an infectious agent is transmitted to susceptible individuals (Hurst and Murphy 1996:6).

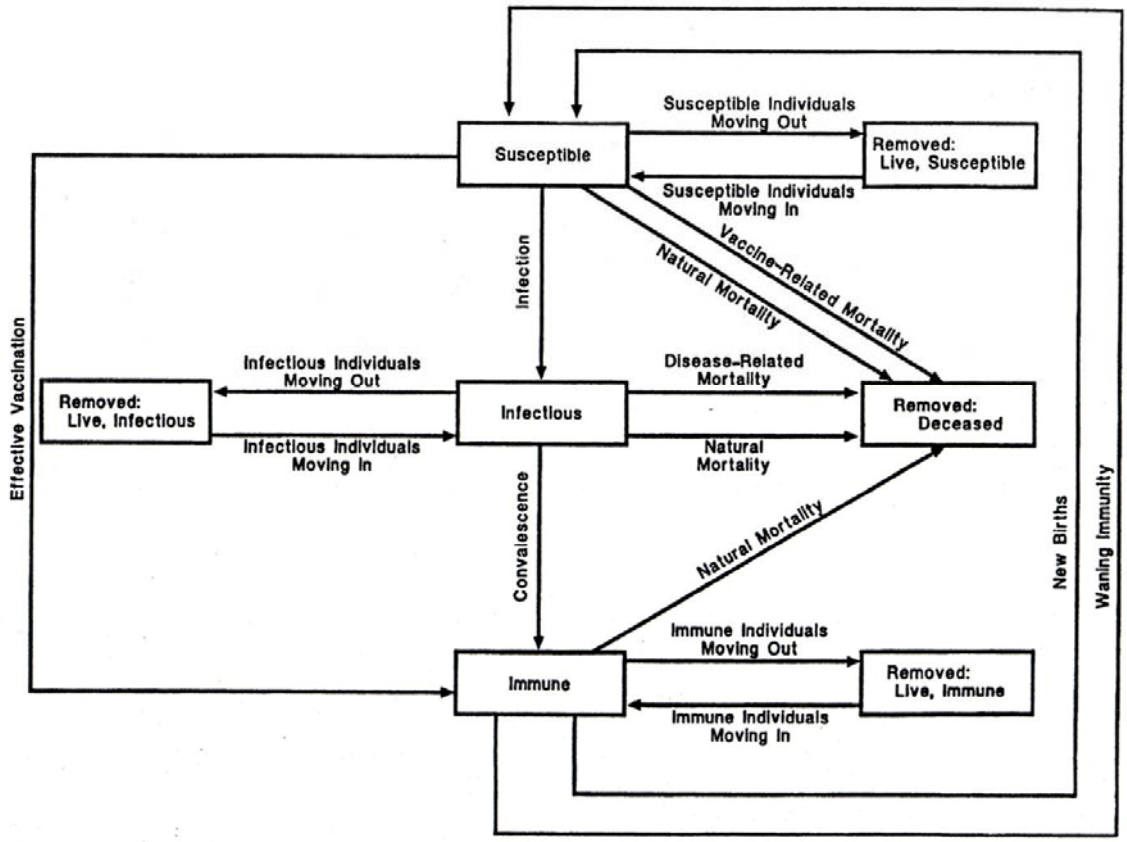

Figure 7: Compartmental model applied to illustrate transmission in a dynamic population. (Hurst and Murphy 1996:7)

The simple model illustrates the basic dynamics captured by a disease transmission model: the whole population is divided in *susceptibles*, *infectious*, and *immune*. An additional compartment of *removed: deceased* is also illustrated. An infectious agent is introduced to the fully *susceptible* population, causing infection. The *infected* will gradually turn into *immune* – or, according to the disease-related mortality, into *removed*. The complex model (which is included here for illustrative purposes only and will not be explicitly described) shows all the aspects of disease transmission that can be represented by a compartmental model. However, in many cases this level of complexity is not feasible, since the parameterisation of the model turns into a challenging task. Another limitation to these complex models is that one may not know all

the details of disease transmission process, at least not *quantitatively* – meaning it may not be possible to estimate the transition rate, vaccination efficacy, or waning immunity. It is important to bear in mind that even though the complex compartmental model provides a detailed description of transmission dynamics, it does so only as a representation, not as a fully grounded model. By this I mean that these early deterministic compartmental models are not satisfactory in expressing the detailed facts of transmission dynamics. They do not take into account the possibility of *chance* in the process, nor are they able to incorporate the variants of vaccines and their effects to the different groups of population (not to mention that they are insensitive to the age and contact-structure of the population). However, to quantify all these facts into the transmission dynamics may be a long and laborious process, as we shall see in the following section.

3.2 Towards adulthood: independent facts using the flexibility of compartmental representations

So, in general terms, compartmental models represent transmission dynamics in a population. The transition rates are usually considered to be deterministic (assuming that all susceptibles turn into infected at rate λ). However, as graphical representations, these models express the transmission dynamics in a clear and effective way. To exploit our metaphor, the deterministic thinking evolves towards the multiplicity of choices in adulthood. This, in other words, is the process of incorporating the detailed facts of the disease transmission dynamics into the graphical representations of population level transmission. Let us explore the following illustrations as steps towards adulthood. Each step utilises the compartmental structure, but takes into account the detailed facts that tell us about the age cohorts, contact-structure, and recovery rates. Figure 8 follows the compartmental structure, but allows the details of the carriage and immunity facts to be expressed. The transition rates between the

sub-groups of “susceptible non-immunes,” “susceptible immunes” and “carriers” are calculated in probabilistic terms.

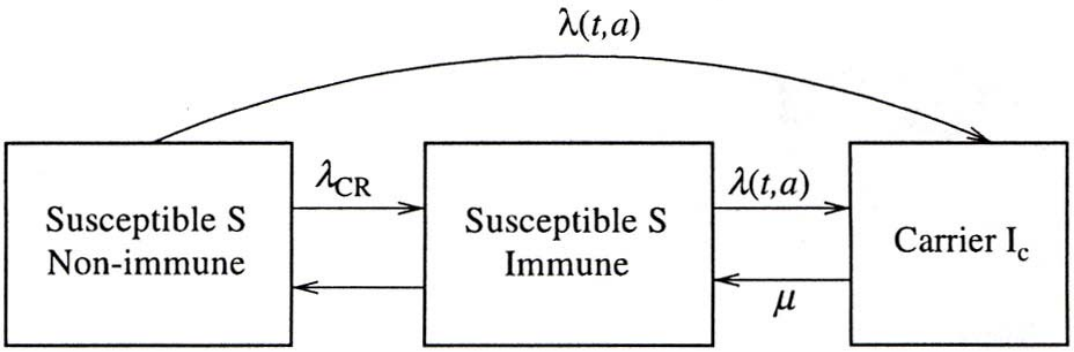

Fig. 3. The model of Hib carriage and immunity. Susceptible individuals acquire carriage at rate $\lambda(t, a)$ [see eqn (1)]. Carriage is cleared with rate μ and the individual turns susceptible again but is immune against disease (susceptible/immune). If Hib carriage or a cross-reactive encounter do not boost immunity, the individual returns eventually to be susceptible/non-immune (see text). Children <2 years old may return directly to susceptible/non-immune. Boosting of immunity in susceptible individuals occurs through cross-reactive encounters with rate λ_{CR}. For simplicity, the figure omits boosting of immunity in Hib carriers by cross-reactive encounters. Disease may emerge in non-immune susceptibles at the onset of Hib carriage.

Figure 8: The transmission pattern of Hib (Auranen et. al. 2004: 950)

To illustrate the detailed level of facts enabled in these representations, we may look at transition rates, which are the set of parameters to express the force of infection, i.e. the rate at which the infection spreads in a population or its sub group. Figure 9 shows this rate in relation to the modelled sub groups of family, school and nursery:

$$\lambda(t,a) = \beta(a)\left[\begin{array}{l} c_f \dfrac{I_f(t)}{N_f(t)-1} + c_d \dfrac{I_d(t)}{N_d(t)-1} \\ + c_s \dfrac{I_s(t)}{N_s(t)-1} + k \end{array}\right]$$

Figure 9: The per capita rate, *force of infection* at which a susceptible individual acquires Hib at time *t*. (Auranen et. al. 2004: 950).

This series of graphical representations to express the transmission dynamics show that the general compartmental model needs to be accommodated to the infection studied. As we have learned from the detailed epidemiology of Hib, transmission dynamics is not a simple process.[19] This has led to alternative interpretations of the transmission dynamics, as the following figure shows:

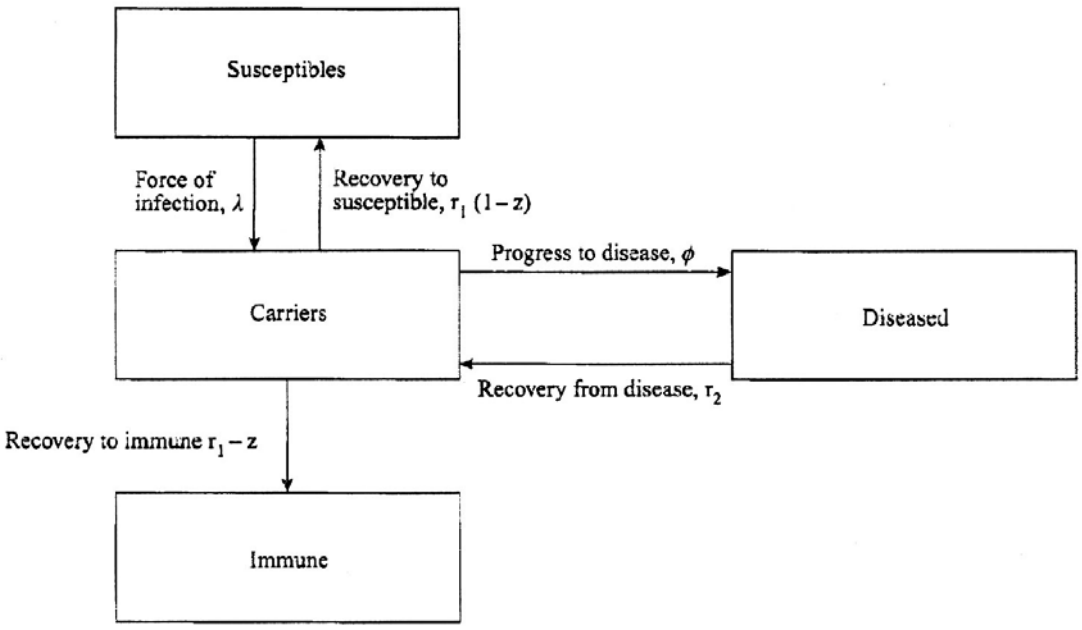

Figure 10: General model of Hib that accommodates the detailed facts of transmission and recovery. (Coen et. al. 1998: 284)

[19] Asymptomatic carriers, non-permanent immunity, age-specificity of transmission dynamics, are details that need to be included in the representation.

In summary: the transition years towards adulthood in the life history of Hib transmission shows *maturity* in two ways. Firstly, the flexible interpretations and accessibility of the graphical representations of transmission dynamics facilitate representing the transmission facts in more refined models (as we will discuss in the following section). They also offer a means of overcoming the difficulties that multidisciplinary audiences often face with respect to the mathematical representation of the transmission dynamics. Interestingly, these representations have also formed the backbone of a graphical user-interface in a modelling tool (a computer programme called Berkeley Madonna). It seems the disease transmission facts took significant steps towards independent adulthood, standing alone (as in these representations) and being open to different interpretations (or generalisations, as we shall see in the following section). Secondly, as the *bloodline* of mathematization through the life history continues, these facts move towards adulthood as they leave the deterministic compartmental representations and accommodate into the probabilistic reality of transmission dynamics. The transition rates between the different compartments are given probabilistic values. This is a clear advantage, since in studying disease transmission in a small population, chance plays a crucial role: the only infected person among the susceptibles may die in a car accident and the threat of outbreak vanish. Furthermore, as we learned in the previous section, the mathematical expressions of the basic reproductive number R_0, the transition rate λ, and other variables are expressed and conveyed to a wider audience with the help of these graphical representations. Considering the challenge faced when the dynamics are domesticated in the simulation model, their simplicity may be deceptive.

We may summarise they key findings in the following table:

Table 2: Transition towards adulthood of facts.

Phase in life history and its description	How do 'facts' lead their lives?	Representations of facts
II Transition from teenage years to adulthood: The II phase shows how 'facts' grow up.	Disease transmission is expressed in compartmental models that serve as accessible representations of the population dynamics.	Established expressions to calculate basic reproductive rate, transition rates between compartments and developing differential equations to express the *change* in rate.

The transitional years from teenager to adult record incrementally widening degrees of independence. In the early teenage years, facts about transmission were still bound within compartments, even though they became independent from their home – the experimental settings of early epidemiology. However, as their independence grew, they became more capable of expressing their detailed character (and raising questions: when do the sub groups of population become susceptible? how do age-specific contact patterns affect transition rates?). With our facts entering adulthood, it is time to explore how the facts of transmission reach the reproductive years – and perhaps have some offspring.

4. The (re)productive years: *Simulated* 'facts' and wider dissemination of the understanding of Hib transmission via modelling

Our facts of disease transmission have grown up and settled down into more stable roles – successful careers and offspring. This section follows how the bundled facts of disease transmission "make themselves at home" with probabilistic simulation models.[20] We will explore one of the most sophisticated forms of mathematical representations utilised by the

[20] This section focuses on models built during 1994-2003 at the National Public Health Institute, Helsinki.

facts: a *structured simulation model*. This model is capable of capturing agent-based dynamics, addressing mixing patterns and including vaccination effects on the circulation and transmission of Hib. As a fine-grained, population-simulation model, it is thus capable of describing the full notion of Hib transmission, immunity, and disease (Auranen et. al. 2004). Our story will take a detailed look at how facts about *transmission dynamics* are nested within the model, and discuss the ways in which these facts become represented, simplified and quantified in the model's assumptions and parameters. The story is told by locating facts of Hib transmission in four models, of which two are strictly speaking addressing transmission and two are tinkering the concept by a more crucial account of it – the prevention of transmission. The data used in this chapter benefit both from documents of published models and the social interactions from the process in which the transmission facts were captured and expressed in those models.

4.1 First steps on the property-ladder: How do facts of transmission enter into the dynamic simulation models?

Finding a home is not always straightforward: your first steps on the property ladder might be a bit wobbly – or you may even struggle to get on to that ladder. Exploring this analogy may illustrate the process in which facts of disease transmission enter the dynamic simulation models on Hib.

As we have learned from the previous sections, *Haemophilus influenzae* type b bacteria is capable of causing life-threatening, invasive disease (such as *meningitis*, *septicaemia*, or *epiglottitis*) – especially in young children. The severity of these conditions is a key factor motivating the quest for a detailed understanding of the dynamics of the infection in order to develop means to control the spread of transmission. As briefly noted, infections caused by Hib have certain features that are challenging for the study of transmission. The natural locus of the bacteria is human

nasopharynx. This locus itself has two implications to transmission. First, it is difficult to define who is a carrier of the bacteria: there are no serological (blood) tests, and taking a sample from the human nasopharynx is a much more complicated procedure than taking a simple blood sample. Second, transmission is easily spread through coughing, sneezing, or close contact between a carrier and a susceptible. Moreover, an individual does not develop a life-long immunity to Hib; on the contrary, after the infection there is only a short protective period before the individual is once more susceptible to re-infection. These general facts about Hib and its transmission in a population were established over the long years of studies on Hib diseases and vaccine development. Mathematization (in the form of developing theoretical epidemiology[21] and compartmental models) benefited from the precise expression of reproductive number (R_0), and force of infection. However, the process of expressing the cluster of Hib transmission facts in an individual-based simulation model on transmission, immunity, and disease is a very detailed process in which the *general* facts are narrowed down and simplified. This process of "finding a home" for facts about transmission in models constitutes a special mode of mathematization, a mode typical for *question-oriented* modelling practices.[22]

4.1.1 From your first flat to the family home: transmission facts nesting[23] in models (1994-2004)

Facts about Hib transmission were established in four models before being translated into the simulation model which allowed the integration of the different aspects of the individual-based disease transmission

[21] As discussed in relation to the early models (Kermack and MacKendrick 1927).
[22] I have described the question-oriented modelling as a process of building and using the models simultaneously in order to answer the questions. I have called the process *tailoring*. (Mattila 2006a, b, c.)
[23] Aashish Velkar has described 'facts' in the process of standardization of measures in 19th C England as 'nested facts'.

process. Let us consider these transitions as a process from buying your first flat through to building your family home. These four models are:

1) the so-called G*oodnight-Kiss Model* (Auranen et. al. 1996), which provides understanding of the simple transmission dynamics within a closed population (e.g., a family);

2) the *Hierarchical Bayesian Model to Predict Duration of Immunity to* Hib (Auranen et. al. 1999), which estimated decline of antibody concentration in order to predict the duration of immunity to subclinical Hib infection and to a serious invasive Hib disease;

3) the *Dynamics of Natural Immunity* (Leino et. al. 2000) that was estimated under different parameters for the force of infection;

4) and finally, the *Model on Immunising Infections of* Hib *and Cross-Reactive Antigens* (Leino et. al. 2002) that was used for explaining the differences in pre-vaccination incidence and age-distribution of invasive disease in different countries.

As the names of these models emphasise, the main aim of the modelling exercise was not to develop further understanding of disease transmission, which – as we learned in the previous sections – was well established. Instead, the focus was to establish the assessment of the preventive and interventionist measures in the models. In the following section, I will explore in detail the process in which the basic facts of transmission establish a home within a simple transmission model. It is also worth keeping in mind that while we dive into the story of transmission, the initial motivation for the modelling effort was argued to be "a need to *understand transmission* of two bacteria, namely Hib and *Pnc*" and ultimately a "need to *plan and evaluate different vaccination strategies*" (Auranen 1999: 9). The need to plan and evaluate different vaccination strategies seems to be the reason why transmission is studied through the explorations of immunity. The understanding of *prevention* of transmission is reached by defining the adequate immunity levels that result naturally (after the disease) or from vaccinations.

It is due to these facts of transmission that the modelling activity aims to study "the transmission in appropriate subpopulations as well as to assess the relative importance of subpopulation and population

transmission" (Auranen 1996: 2235). In other words, the study aims at examining transmission in terms of estimating the transmission rates within a family and a community in relation to Hib infection. To understand why transmission is worthy of its own model, we need to know further details of the infection itself.

If we turn to look at what happens to the facts in relation to the model built to estimate the family and community transmission rates of Hib, we notice an important characteristic. The relatively general, hardcore facts about transmission given above become more detailed and encrusted with new knowledge about the carriage of Hib. The model affected the facts it incorporated by predicting the prevalence and incidence of Hib carriage as a function of the family size and age structure (Auranen 1996: 2251). This means that what first occurred as general features of the transmission were now *narrowed down* and *sharpened* to show us that families with children of certain age-groups (those in day-care or at school) are more likely to harbour the infection, which also explains the apparently arbitrary occurrence of the infection in adult population. The transmission happens within the family through casual physical contact, such as goodnight kisses (hence the model that bears this name). Although incomplete, this model becomes a "first flat" for our facts, and we may now consider the prospects this opens for a more permanent home.

4.1.2 Goodnight-kiss model as the "first flat" for transmission facts – and as a promise of "family life." (1994-1996)

Transmission facts were first reported in a statistical model of transmission of Hib bacteria in a family.[24] They were discussed in a following way in the introduction of the article:

[24] In Auranen et. al.(1999), this model is also called a Good-night kiss model.

> The transmission of many infectious agents requires close physical contact between a carrier of the agent and a susceptible individual. Consequently, a high prevalence of infection can sometimes be observed in groups of close contacts, for example, in members of a family or in children attending the same day care facility, while the prevalence in the population at large is low. To understand the dynamics of such an infection and to evaluate the ability of the infection to persist in a population, it is therefore important to study the transmission in appropriate subpopulations as well as to assess the relative importance of subpopulations and population transmissions. (Auranen et. al. 1999: 2235).

This quotation contains two specific facts about Hib transmission. It tells us something of the act of transmitting the bacteria (i.e., that it requires close physical contact between a carrier of the agent and a susceptible individual) and it reveals an apparently contradictory feature of the infection, namely "a high prevalence observed in groups of close contacts while the prevalence in the population at large is low" (Auranen et. al. 1996: 2235). It seems that this contradictory feature actually initiated the early processes[25] of tracing the details of transmission. In previous studies[26], I have shown that the goodnight-kiss model was not only an exercise to study the particulars of transmission in a closed population, it also promised an *integrated simulation model*, a "family home" for offspring facts. What do I mean by this?

As mentioned, there was a need "to understand transmission and to plan and evaluate different vaccination strategies" – in other words, to produce, interpret, and disseminate facts about Hib transmission dynamics in order to examine how to prevent it. Yet the bundle of transmission facts were not easily settled in a model that required simplification of the fine-grained details of transmission process, linkage with data, and ways to express the changing states between susceptibles

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[25] These processes took place in the early seminars of the INFEMAT project (the project that specialized in developing the computer-models on infectious diseases during 1994-2003) jointly with the University of Helsinki, the National Public Health Institute and the Helsinki University of Technology.

[26] Mattila 2006a, b, c.

and carriers. So the Good-night kiss model was only a first step – the first flat: Not a perfect solution, perhaps a compromise with location and cost, but still, a way for us to say that the facts were leading independent lives.

4.2 Family life: reproductive years and offspring facts

If we appear to observe how the life of facts about disease transmission continues in the models, we notice that the early formulations of Hib-transmission in the goodnight-kiss model offered the promise of a more stable home. The basic idea of modelling transmission in a family linked into the tradition of examining infectivity of diseases in households. This is an important context from the public health point of view, because households are the units where different age-groups come together and transmit infectious agents from their various contact sites.

> Household studies can be used to assess the type and the strength of the infectivity of transmittable diseases. The corresponding statistical models are usually formulated for infections which yield immunity against reinfection, either for lifetime or at least for an epidemic season. To estimate secondary attack rates, it is then possible to specify models without explicit reference to the dynamics of the infection process. In the present study, such an approach does not apply, because pneumococcal carriage is recurrent. An explicitly longitudinal model formulation was necessary to capture the dynamics of carriage transmission. (Auranen et. al. 2000:1051)

Focussing on the family unit can explain sudden outbreaks of infection within adult population. Since the clinical motivation to understand Hib carriage across different models was central for the project, we could say that *transmission* facts hence settled down for (what became) their reproductive years through these activities.

From the epidemiology, we learned the key features defining Hib transmission, but what did we learn from the domestication of these facts in the goodnight-kiss model? The opportunity to produce offspring emerges here as a process of compromising or filtering the knowledge in

order to model the full, complex picture of Hib transmission. This requires an understanding of the different types of vaccines used, concentration of antibodies, and the dynamics of natural immunity. However, the exploration of how our facts "settle down" during the early years of their adulthood shows us that a vast background knowledge on disease transmission is needed in order to be modified for the modelling purposes.

4.3 Offspring facts of transmission

From knowledge about disease transmission carefully established during 1993-2000, the facts moved on. In 2004, transmission settled down in a simulated "family home," which means they were taken into an individual-based population simulation model that studied transmission, immunity and vaccination effects in relation to Hib. It is finally time for *offspring*. By offspring I mean to refer to the *next generation* of facts, which are potentially more flexible and transferable across the domains, perhaps capable of expressing something beyond their parents (like accommodating into new cultures).

The explorative simulations are anchored firmly to the epidemiological ground:

> Transmission of Hib occurs through asymptomatic carriers. Most episodes of Hib carriage pass without clinical symptoms, and only in rare cases does carriage proceed to invasive disease (e.g. meningitis or epiglottitis). Therefore transmission of asymptomatic nasopharyngeal carriage lies in the focus of investigation of Hib epidemiology. Transmission in turn is influenced by the recurrent nature of carriage acquisition and the typical clustering of Hib carriage in family and day-care settings. (Auranen 2004: 947)

The ethnographic data[27] from the building, calibration, and testing of the simulation model broadens the perspective on how facts about transmission finally settle down into the simulation. Using ethnographic

[27] The analysis is based on chosen transcripts from meetings that took place during 2002-2004.

data obtained between 2002-03, the following section briefly analyses the ways in which facts about disease transmission are implemented within the simulation model.

The basic aim of the modelling activity is to come up with a transmission model. This task is neither obvious nor easy, even though in the final stage it is only *one part* of the more complex model.[28] For those working on this problem, there is no guarantee that the process will succeed (in one meeting, the achievability of transmission model came under doubt: do we have a transmission model or do we not?). As we have seen, disease transmission is a manifold concept. In the modelling activities, it was disentangled, unpacked, turned into smaller pieces with the help of auxiliary tools (e.g. representations of transmission patterns, estimates of natural immunity etc.). One of these tools is called *force of infection*, which is defined as the rate at which susceptible individuals become infected by an infectious disease (the force of infection is often notated with λ). The auxiliary tools are essential, as they force the process of mathematization to take into account the contextual specificities, such as type of infection, population structure, and age dependency. Beneath the transmission model there is a population model. But turning this into a dynamic, growing population implemented with a S-I-S-mechanism turned out to be problematic. When the modellers encountered a bug in the population simulation programme, they chose to "freeze" the population (that is, to model it *without* growth dynamics). The S-I-S-pattern was nonetheless introduced into the frozen population, but the S-I-S-pattern was, at this phase, limited only to carriage (immunity was forced artificially to result from the disease). A month later, in order to specify the infection caused by Hib and infection caused by other bacteria, exposure to cross-reactive bacteria was added to the model. Exposure to cross-reactives is likely to boost an individual's

[28] Mattila 2006.

immunity. This interferes with the short period of immunity, caused by Hib (which will gradually turn back to susceptibility).

The interactional data tells us that despite the long-term efforts to house facts about transmission within the models, it is still not quite clear to everyone what transmission actually *is*. The following extract from ethnographic observations underlines this problem:

> In late 2002[29], a computer scientist posed a crucial question in the meeting: "What do we actually mean by transmission?" And the answer reveals the usage of auxiliary concepts in order to reach the fact itself.
>
> Statistician: Well it means that we calculate through all contact sites according to the simulation model. And then we look, one individual at time, as we do in that [the model]. What is the force of infection with this individual? We have thought that it is the same all the time, the average force of infection. This is something we can calculate from the data [we have]. And I have tried that and used the best parameter values I have had chance to estimate, and it seems to work quite well."
> Computer scientist: Okay.
> Statistician: So, in my opinion, I was sort of convinced that this works well, this transmission model. That we actually have the transmission model. And we have good parameter values and then we feed in/put in/implement CR [cross-reactives] as "background radiation," on a stable, constant level, and it produces this disease.
> Epidemiologist (junior): …and then there would be the variation required. That you have a constant CR and added Hib, as it is.
> Statistician: Yes. But then among adults it means that it is only CR all the immunity we have, because Hib is reduced to so small a level.

Thus we see that facts about transmission do not passively settle, but need instead to be actively settled in the model. Be that as it may, as *facts* they also reveal surprising sensitivity: in a long discussion, just a couple

[29] Meeting at National Public Health Institute, 17.11.2002, (001/22:35). Statistician is a post doc researcher, computer scientist is a senior researcher.

of months later in early 2003, the testing and calibration activities were resumed. The transmission model was now subjected to preliminary evaluation by comparing the model-based results with the existing (real-world) knowledge on Hib-transmission as documented in the literature. And these comparisons again revealed new sides to the facts: they were sensitive to the population in which they occurred. So even though the discussion was limited to Hib transmission, factors such as the different scheduling of vaccinations, different age structure in day-care and school groups, and different levels of CR, varied depending on the country or region in which the study was conducted. It emerges that the facts of transmission are not simply reproducing themselves exactly – since to do so would be to rigorously mimic the trends of the Finnish population, vaccination plan and CR exposure on which the model was based. This was discussed in terms of how well the model explains the known specificities of transmission in different countries (in Gambia and in the UK).

> Epidemiologist (7.3.2003:001/58:07): … so when we talk about these day-care groups and so on in relation to transmission, it is all relevant. So what they try to say is that in the developing countries, like in Gambia, from where we have the "carriage data," all transmission has happened before the day-care age. But yet these data are not enough. So the study showed that the carriage is higher than here already during the first and second year of age. … And we also thought in the comparison between Finland and England that the disease occurs earlier than with us and … we sort of explained that with CR.

As we see from this process, to bring in the details of transmission dynamics in a specific population led to modelling practices that elaborated the transmission dynamics in detail. However, if data are scarce or absent, or if behavioural and mixing patterns are not clearly documented or widely heterogeneous, domestication may be difficult, and the transmission dynamics remain to be explored only in a more general

level. This, in the end, may diminish the usefulness of modelled evidence (or leave unintended uncertainty in the models). Of course, the generalisability of a fact could be considered as a form of its *seniority*. Some levels of that maturity were reached in the models, even though they were tailored to represent only the Finnish population.

In summary: this phase has shown that facts of disease transmission may find a home within a simulation model as summarised in the following table.

Table 3: Summary of the III phase in life history of facts.

Phase in life history and its description	**How do 'facts' lead their lives?**	**Representations of facts**
III Reproductive years: This phase describes how the *general* facts are expressed in computer-based models, reproduced in order to study specific aspects of transmission.	Transmission facts are *housed* in a set of models that clarify the details of transmission dynamics.	Mathematical models and computer simulations as form of mathematization. Probabilistic approach to increase *reality* of transmission dynamics.

So in this life-history, our facts finally found their way to a stable home. Their first, temporary lodging captured the enthusiasm of independence from earlier nurturing environments.

4.4 Dual nature of disease transmission – further offspring facts

Let us turn back to our special case of Hib and the transmission facts established by the models. As discussed previously, the main interest remained the *prevention* of transmission. In order to be able to calculate the preventative levels of antibodies to minimise transmission, three models were built to domesticate the general facts of immunity to Hib and to accommodate these facts in the available scenery provided by the data. These models remind us of the dual nature of disease transmission.

Even though the public health measures aim primarily to prevent transmission, transmission is also the force that induces immunity in the population. In order to optimise the preventive measures (vaccinations), one needs to learn from the side effects of the possible decrease in natural immunity against the disease that was sustained by the circulation of the bacteria. Understanding of the protective side of transmission was established in three models studying the varying relations of cross-reactive bacteria (i.e. bacteria that are circulating in a population and boosting immunity) and antibody levels acquired by encounters with Hib bacteria.

The first model, which aimed to predict the *duration* of immunity to Hib, established the decline rate of antibody concentration. It revealed the fact that the dynamics related to antibody concentration have important implications in predicting the consequences of different vaccination programmes (Auranen 1999). Hence, prevention of transmission by polysaccharide vaccines was observed by establishing the decline rate of antibodies in the model. Interestingly, the applicability of these observations reaches other bacterial infections with *similar antibodies*, i.e. pneumococcal and meningococcal infections. Hence, transmission, even though domesticated in this model as a characteristic of Hib, is generalisable to other infections.

The dynamics of natural immunity model became an icon for later estimations of the different levels of force of infection and evaluating their impact on the duration of natural immunity. The principle idea was to explain the increase in numbers of invasive disease in unvaccinated cohorts. However, the usefulness of the estimated forces of infection was that these numerical estimates were applied in an attempt to simulate the transmission in an agent-based model. Once again, the exploration of natural immunity aimed at “optimising vaccination strategies,” which was claimed to be the major aim of infectious disease epidemiology (Leino 2000: 583). Furthermore, this general aim can be translated into two

specific steps: minimising incidence of invasive Hib disease at a population level, and diminishing the number of colonisations (i.e., those environments where Hib protective antibody levels are below the estimate) by vaccination. This leads to a model-based observation of transmission: there is a connection between the rate of decline of antibodies and the force of infection that may have implications to the population level immunity (so called herd immunity). This connection means that if the force of infection is low, vaccination may decrease the circulation of Hib bacteria and hence strengthen the herd immunity. On the other hand, if the force of infection is high, the vaccination may cause incidence of invasive disease in unvaccinated cohorts. Hence, the transmission itself is altered, which have indications for vaccination planning. (Leino 2000: 589).

Furthermore, to understand the infection dynamics and the role of other circulating bacteria, the model on natural Hib infection dynamics and the role of cross-reactive antigens to estimate the total rate of immunizing infections of Hib and CR prior to wide-scale vaccinations was built. This model explained, again, one aspect of disease transmission: the frequency of CR contacts may explain the differences in the pre-vaccination incidence and age-distribution of invasive disease in different countries (Leino 2002: 73).

So, these models elaborated, housed, and reproduced facts about immunity; an immunity which protects and prevents the circulation of the transmission. Each of these models told a different story of its own, but *together* they nurtured an understanding capable of reaching realistic estimates to prevent transmission. In a way, they revealed the dual nature of transmission that needed to be fully understood. Transmission is not only causing a threat of severe disease, it also has a protective purpose – and interfering with this cycle (by vaccinations) may alter the delicate balance and cause new cases of disease in older age-groups. Hence, this side of transmission underlines clearly the complexity of drawing the

whole picture of disease transmission and domesticating it in models. It also reminds us of the initial public health perspective, discussed earlier: it is not enough to explain the singular causes of disease but to expand the explanation to cover the causes and effects of disease transmission in a population.

The dual nature of transmission: as a threat and a promise of prevention may remain invisible for the public. Yet, for the public health authorities, facts of transmission, from early on to those established and elaborated in the models are seniors, respected for their information content, their capability of being a reference point in decision-making. This phase in the life history of facts shows us that the bundle of facts is not easily expressed in mathematical models. The complex, multivariable nature of transmission dynamics requires simplifications and modifications in order to be entertained in the simulation model. Yet we have one period of life still to explore: seniority and the potential passing away of facts.

5. Seniority and passing away: from the modelled world to the developing world

The analogy with old age captures two aspects of the life of facts: either the facts reach a respected position, or else they are closed away and forgotten. In common terms, we might think of the elderly reverentially, as repositories of accumulated wisdom; or we may instead regard their useful life as spent, and sequester them in homes, forgetting them in the hubbub of our everyday duties. In this section, the seniority of facts and their passing away will be discussed from two perspectives. Firstly, once we have learned from disease transmission and especially how it is captured in the models we have also learned that the interventions to prevent transmission have been successful. In the Western countries, incidence of Hib diseases has fallen significantly. At the same time, there is growing concern about the collateral harmfulness of vaccinations. In

the UK, this concern exploded with the MMR vaccine, but it will surely also have impacted on the more general acceptance of vaccines, and thus on parents' willingness to bring their children to be vaccinated. Where the wholly beneficial character of vaccines was previously accepted as a fact, this scepticism and doubt can be interpreted as one way of *forgetting* the fact or of the fact *passing away*. Another way of looking at the obsolescence of facts is by reflecting on the unequal distribution of Hib vaccinations in national vaccination strategies. Thus even after Western countries have eradicated the problem of disease transmission, it may still continue to be a continuous threat in many parts of the world. I will discuss the potential of the simulated facts to keep the problem in our minds, and develop tools for public health advisory work on reshaping their vaccination policies.

For example, the following graph tells us of the success story of implementing *Haemophilus influenzae* type b vaccine in England and Wales. The descending trend of Hib diseases (cases) is reassuring of the efficacy of the vaccine. Why call it a success story? To recap, Hib is the leading cause of bacterial meningitis, causing also other invasive diseases, such as pneumonia and epiglottitis.

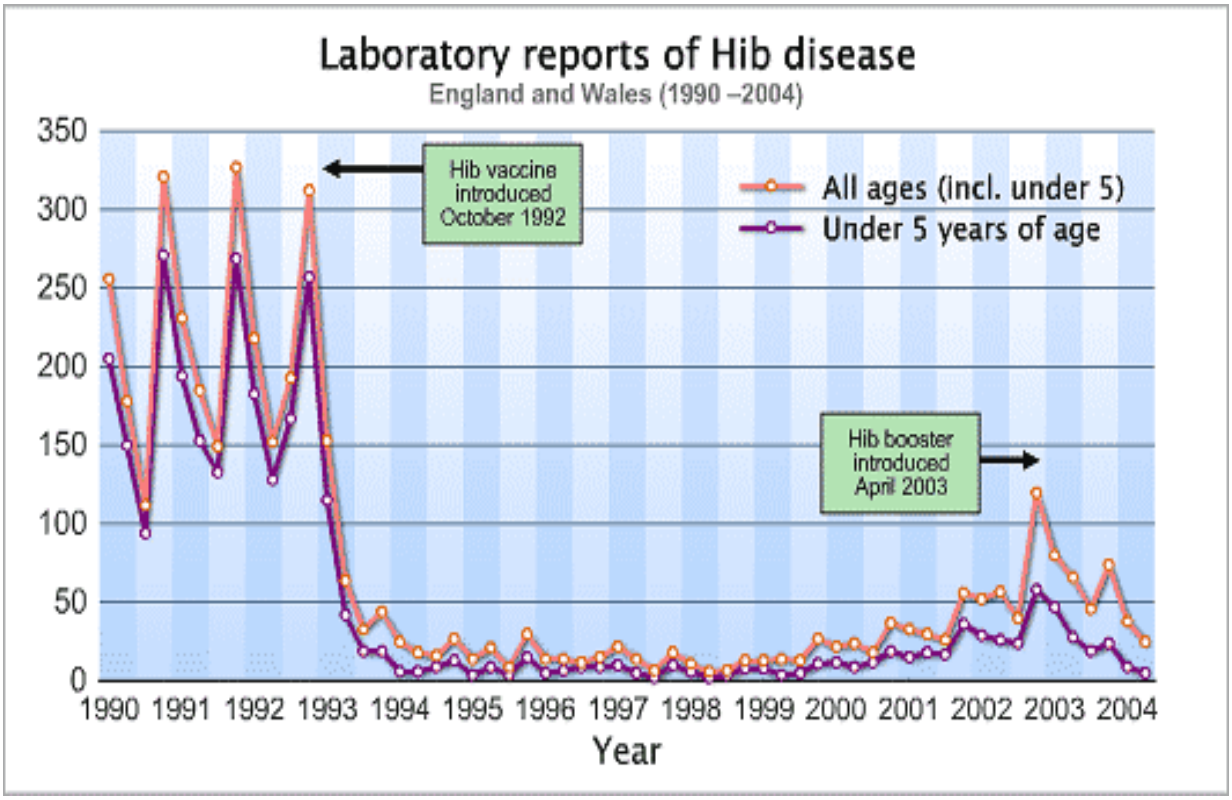

Figure 11: NHS laboratory report of Hib disease in England and Wales shows the efficacy of vaccinations. (NHS Immunisation information. www.immunisation.nhs.uk/.../How_common_is_Hib)

The question is: if the disease and its threat (or severity) disappear due to the implementation of vaccinations, does the fact of its transmission pass away? I am prone to think that *passing away* of a fact might actually be something like that. The fact itself, the knowledge, may not vanish – it disappears from our minds, is forgotten, and passes away. We feel that we are protected and safe, due to vaccination – and vaccine induced herd immunity. It is this crucial moment when individualism raises its head. We are safe, the images of children suffering from meningitis have disappeared, and we begin thinking – What if the vaccine is not safe? What if my child is protected in any case, that the threat of transmission has died? The most recent case of anti-vaccination movement among parents is of course documented in relation to MMR vaccinations, mid-1990s.[30] But the brutal logic of herd immunity does not allow free-riding,[31]

[30] Cf. Collins and Pinch (2005).

and the transmission is liable to return if the protective level falls. We may, moreover, think of another consequence of our 'short memory'. Once the threat of disease transmission is cleared from our minds, we may also forget those societies that continue struggling with it. The following map tells us of the ongoing public health problem identified in the grey areas. There are still approximately 3 million cases of serious diseases with 400-700 000 deaths annually in infants aged 4-18 caused by Hib and *Bacterial meningitis* represents 52% of all these infections.

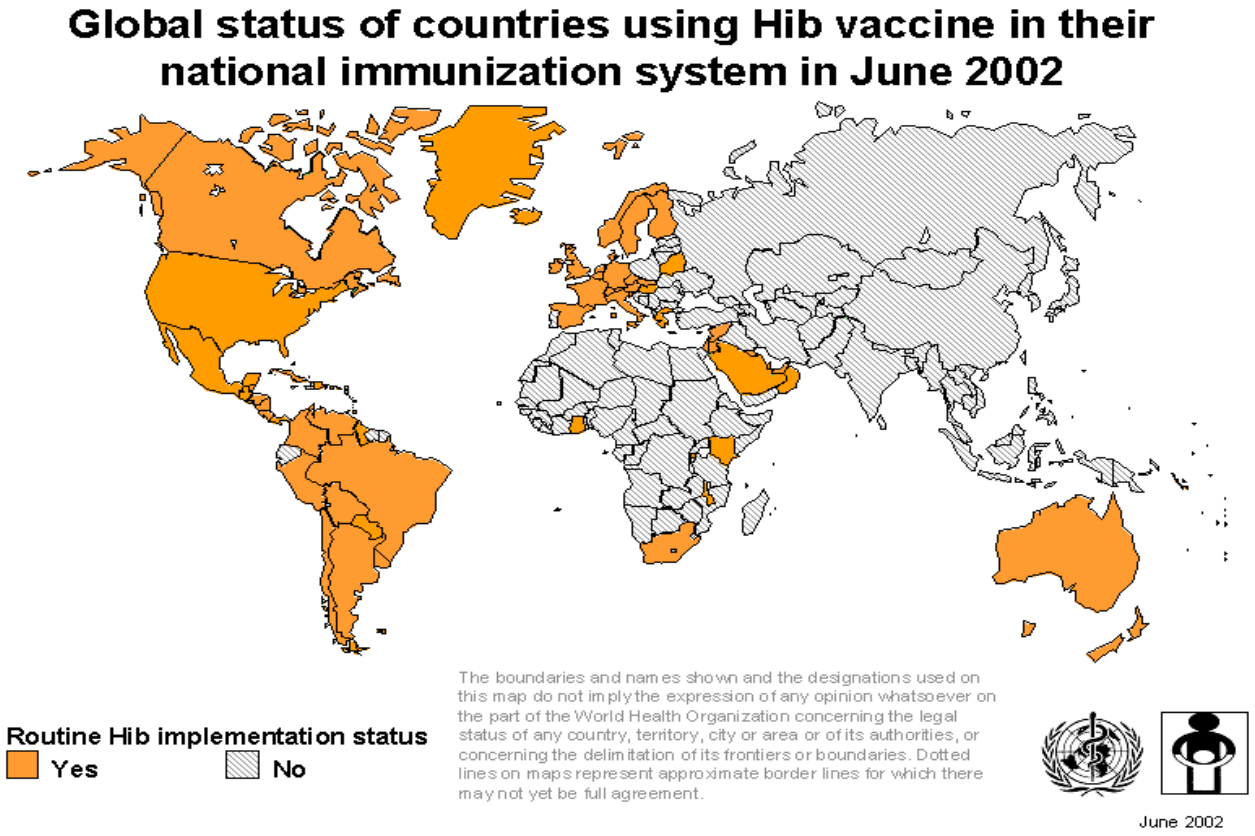

Figure 12: WHO map of countries using Hib vaccine in 2002. (WHO: Department of Immunization Vaccines and Biologicals Vaccine Assessment and MonitoringTeam)

[31] Free-riding is a game-theoretical strategy in which one individual benefits without bearing the costs if she refuses to follow the actions taken by others.

To use simulation models as administrative tools, not only in production of evidence for current vaccination policies in our society, but as public health tools to help to optimise vaccination strategies in the developing world, was one of the primary goals of the Helsinki modelling project. In other words, to create a general tool for a variety of purposes in order to overcome the problem of unavailable surveillance or serological data. But the challenge remains to persuade the countries in the *grey* map to include Hib vaccinations into their strategies. In this quest to colour the map, the simulation models may function as flexible and useful tools to carry the *senior* facts of transmission to other domains. In other words, as expressed in Leino (2003:10):

> In the developing world data on the disease burden are limited and although WHO and GAVI[32] advocate Hib conjugate vaccination, the major question remains whether universal vaccination will be at all feasible in the poorest economies. Will it be cost-effective, and, moreover, will it be an appropriate use of resources among other possible health interventions? Schedules optimising the age of vaccination and the number of doses are crucial for the acceptance for the expensive conjugate Hib vaccines. [...] Ultimately information on Hib transmission allows predictions to be made of the effects on the population level following large-scale vaccinations.

This is clearly a strong reminder of the fact that is about to pass away. It also explains the rationale behind using models to refine and domesticate the facts, and to overcome the possible shortcomings with available data. The modelled facts of decrease in transmission, the vaccination coverage needed for optimal herd immunity level, and the falling number of severe cases should convince the decision-makers of the necessity of vaccinations. It is through the *seniority* of these facts, their generalisability despite the fine details of their modelled context, that they are imbued with sufficient persuasive power to fight against superannuation. Nonetheless, finding a balance in this matter remains an open-ended challenge.

The following table summarises the main aspects of seniority and passing away of transmission facts:

Table 4: Seniority and passing away in life history of facts.

Phase in life history and its description	**How do 'facts' lead their lives?**	**Representations of facts**
IV Seniority and passing away: The phase exploits the idea of *aging* fact, with the flavour of *forgotten* fact (as we are blamed to forget our elderly); passing away refers to the idea that a fact may disappear, die, pass away from our consciousness	Seniority of a fact refers to its generalisability. Some of the *simulated* facts reached seniority and were potentially useful for studies of other infectious agents. Passing away happens, when the facts of the threat of the disease disappear from our minds: effective vaccination policies have swiped away Hib disease from our societies and yet the developing world tries to cope with the disease burden.	Data and mathematical models to describe the transmission dynamics in the developing world are scarce.

In summary: this characterisation of the *seniority* of facts embeds a double (and self-negating) meaning: old facts *either* hold respected positions, *or* else are something to be excluded from the current affairs. In the question of disease transmission, public health authorities seek advice and evidence for decision-making processes from senior facts, from knowledge claims that contain information applicable to different contexts. Yet, faced with monotonous claims for a continuous threat of transmission, the lay public easily disregards such information, shunting it into what might (by our lights) be called *retirement*. Out of sight, out of

[32] The Global Alliance for Vaccinations and Inoculations.

mind – and the legitimacy is found for free-riding strategies in vaccination decisions.

There are, however, other aspects to the passing away of facts. Once they pass away from our minds, they potentially pass away from the lists of funding priorities – leaving those countries and populations at risk. New vaccines that are implemented in Western programmes are often prohibitively expensive for the developing world. Perhaps it remains an open challenge to write the *family histories* of disease transmission and to remember the benefits of preventive measures.

6. Discussion

This discussion will reflect on the initial frame – that is, on the concept of life-histories. We will discuss how this concept, through the analysis above, has helped us to better understand the evolution of factual concepts and the stepwise process of understanding disease transmission, and, finally, what that concept is actually telling us about how well facts travel.

As an analytical frame, what has “life history” offered us? On the basis of the table, we can summarise that in each phase, knowledge – facts – are refined, sharpened, circulated, and domesticated in a particular way to carry on with their lives. Key to these heterogeneous practices are the mathematical representations. From the early observations of transmission in a population, through the flexible graphical representations of compartmental models, to the fine-grained simulation models, the facts of transmission dynamics are expressed in mathematical terms. Life-history (as a frame) not only shapes the linear timeline of the developmental process, it also allows us to observe the different aspects of how facts live their lives. Maturation towards *seniority* is expressed in terms of the generalisability (the epistemic scope) of the knowledge available. *Passing away* indicates the moments when the fear of disease transmission disappears from our minds – waiting for the

moment to reappear when our herd immunity threshold falls. Life history, however, is more than just an organisational frame: it can be linked with the methodological aspects it permits us to take into account. This means that elaborating a life history of facts actually allows us to use multiple sources of data, to move smoothly between the micro-level interactions in modelling practices, and the more general public health studies documenting the major characteristics of transmission (e.g. Frost's transmission vehicles). And, as the micro-historical tradition acknowledges,[33] through the detailed stories, we may learn something surprising or controversial from the more general phenomena. It seems that the idea of knowledge production, which is well documented and discussed, [34] has led us to believe that, once produced, knowledge or facts are simply "out there," ready to be used. However, the mutual development of the early understanding of transmission dynamics, the difficulties in identifying the bacterial agent in the first place, and the growing awareness of the population level dynamics tell a different story. Even though the knowledge of germs as causes of diseases was produced, it was not a comprehensive fact to explain all the details of transmission – further research and further observations were necessary. In a similar way, once the transmission patterns were successfully captured in compartmental models, the deterministic relations between compartments were unsatisfying when the aim was to understand transmission dynamics in small populations. And if we were to think that by the mid-1990s the secrets of Hib transmission were revealed, the efforts of nesting these secrets in offspring facts from computer-based models surprise us. It was not a smooth and simple process, on the contrary, after a set of 5 models, the fine details were tamed in the agent-based simulation model that was, however, capable of telling the story of transmission in a Finnish population.

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[33] Cf. Ginzburg (1989).
[34] E.g. Latour and Woolgar (1979/1982), Knorr Cetina (1981).

Through the life history of facts, we have been able to trace some moments of the development of epidemiological knowledge and its dependency on the mathematization in order to address the population level effects. Even though we may think that the threat of transmission has passed away, it may, however, as characteristic to most epidemiological phenomena, lead us back to the birth. Hence, the facts of disease transmission continue to live among us.

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