# Documentation of TBRiederEpiFlash

Version: April 7, 2011

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Introduction | 0_00 | Inventory |
| | 0_01 | Introduction |
| | 0_02 | An epidemiologic model of tuberculosis epidemiology |
| | | |
| Exposure | 1_00 | Introduction to exposure to *M tuberculosis* |
| | 1_01 | Exposure outdoors and indoors |
| | 1_02 | Survival of tubercle bacilli outdoors |
| | 1_03 | Role of general population age structure |
| | 1_04 | Role of tuberculosis population age structure |
| | | |
| Infection | 2_00 | Introduction to infection with *M tuberculosis* |
| | 2_01 | The production of droplets |
| | 2_02 | From droplets to droplet nuclei |
| | 2_03 | Measuring infection: the tuberculin skin test and its interpretation |
| | 2_04 | The indicator: annual risk of infection with *M tuberculosis* |
| | 2_05 | Incidence vs risk of infection with *M tuberculosis* |
| | 2_06 | Risk of infection with *M tuberculosis* and trend in Europe |
| | 2_07 | Prevalence of infection with *M tuberculosis* in Switzerland |
| | | |
| Tuberculosis | 3_00 | Introduction to tuberculosis |
| | 3_01 | Risk of tuberculosis given infection by time elapsed since infection |
| | 3_02 | Lifetime risk of tuberculosis |
| | 3_03 | Age as a modifier of tuberculosis risk given infection |
| | 3_04 | Sex as a modifier of tuberculosis risk given infection |
| | 3_05 | Sterilization of primary infection |
| | 3_06 | Role of exogenous infection in pathology |
| | 3_07 | Primary, endogenous reactivation, and exogenous re-infection tuberculosis |
| | 3_08 | HIV infection as a contributor to morbidity |
| | 3_09 | Quality epidemiological surveillance |
| | 3_10 | Sex ratio over time |
| | 3_11 | Contrasting morbidity in two countries |
| | 3_12 | Tuberculosis among the foreign-born |
| | 3_13 | Morbidity cross-sectionally and by birth cohort |
| | 3_14 | Projecting tuberculosis from birth cohorts |
| | | |
| Death | 4_00 | Introduction to death from tuberculosis |
| | 4_01 | Fatality of untreated tuberculosis, by microscopy |
| | 4_02 | Cumulative fatality in three European countries |
| | 4_03 | Mortality in three European cities |
| | 4_04 | Morbidity-to-mortality ratio |
| | 4_05 | Mortality from tuberculosis cross-sectionally and by birth cohort, males |
| | 4_06 | Mortality from tuberculosis cross-sectionally and by birth cohort, females |
| | | |
| Summary | 5_00 | Summary |
| | | |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Introduction | 0_00 | **Inventory**<br><br>*0_00-1.wav*. Access the different sections and any clip within the section from this inventory. If you are a first-time user, we recommend starting with the introduction which also informs you how to navigate around. In any section and clip you can return to this inventory. |
| | 0_01 | **Introduction**<br><br>*0_01-1.wav*. Welcome to this presentation about the epidemiology of tuberculosis. Its purpose is to provide you with insight into the dynamics of the tuberculosis epidemic over a prolonged period of time. For its illustration we have purposefully chosen data that are largely from western Europe, supplemented as required by data from other sources. These data provide a wealth of information covering a time span over more than a century.<br><br>*0_01-2.wav*. You may move at any time to the next part within the current clip, to the next clip, or to the inventory by clicking the respective icon at the bottom. |
| | 0_02 | **An epidemiologic model of tuberculosis epidemiology**<br><br>*0_02-1.wav*. To facilitate the understanding of the epidemiology of tuberculosis, we use a conceptual model that is intuitively simple to understand, yet sufficiently detailed. Best fitting our requirements is the tuberculosis classification of the American Thoracic Society.<br><br>The first in the chain of events is exposure to *Mycobacterium tuberculosis*. Pragmatically, we define exposure as a situation in which an individual is breathing air which contains a sufficient number of tubercle bacilli that will result, with a reasonably measurable probability, in inhalation of these, given a sufficient amount of exposure time to that air.<br><br>*0_02-2.wav*. Given a sufficient amount of exposure time to ambient air containing *M tuberculosis*, the exposed individual may inhale tubercle bacilli that may reach an alveolus. If *M tuberculosis* adheres to the alveolar cell lining, a tissue macrophage will ingest it like any foreign body and transport it into the lung tissue. *M tuberculosis* seemingly possesses the ability to prevent phago-lysosome fusion or to escape from its effects and thus prevents its own destruction. It retains its net ability to replicate within the macrophage, then destroys the host cell and the released bacilli are engulfed by other macrophages. Tubercle bacilli will be transported via the lymphatics, gain access to the blood stream and disseminate throughout the system. This establishes a latent or sub-clinical infection in the host.<br><br>*0_02-3.wav*. After a median of about 6 weeks following entry of the bacilli, the cellular immune system has been readied to mount a specific response, resulting in activation of the macrophages. This response generally brings replication of bacilli to a halt and results in targeted killing of tubercle bacilli. It is not known in what proportion of infected persons all bacilli are eliminated, but it is known that complete elimination is not always accomplished and in some individuals some bacilli remain alive for weeks, months, years, or even decades.<br><br>*0_02-4.wav*. In a certain proportion of infected persons there is direct progression to overt clinical tuberculosis. A progression within the first five years has been termed primary tuberculosis, a progression occurring later, |

| | | |
|---|---|---|
| | | endogenous reactivation tuberculosis. Of epidemiologic interest is the distinction between transmissible and non-transmissible forms of clinically manifest tuberculosis.<br><br>*0_02-5.wav*. The final event of progression through the stages is death from tuberculosis.<br><br>*0_02-6.wav*. Known and even more unknown factors increase the risk of progression from one to the next stage in the chain of events. |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Exposure | 1_00 | **Introduction to exposure to *M tuberculosis*** <br> *1_00-1.wav*. Exposure is the prerequisite for any subsequent event. Exposure takes place when an infectious source case expels tubercle bacilli into the ambient air in which the exposed person is breathing. If there are no incident sources of *M tuberculosis*, exposure risk will cease. Given a fixed number of incident source cases, the most important modifier of exposure risk in the population is duration of infectiousness of source cases: a shorter duration limits the number of possible source-contact encounters, a longer duration increases the number of such opportunities. The product of incidence and duration is person-time of infectiousness in the community. Tuberculosis prevalence surveys measure this combined effect but do not easily allow disentangling incidence and person-time. Even if the total amount of person-time of infectiousness is fixed, exposure risk is further importantly modified by the number of possible case-contact encounters per unit of time of infectiousness. An example would be the differences in population density between rural and urban settings, where the latter is conducive to allow a much larger number of such encounters than the former. |
| | 1_01 | **Exposure outdoors and indoors** <br> *1_01-1.wav*. We have defined relevant exposure as breathing air that contains a sufficient number of bacilli as to result with some reasonably measurable probability in infection with *M tuberculosis*. If we examine this a bit closer we note that outdoors and indoors are two distinctly different situations. Tubercle bacilli expelled outdoors are instantly diluted in a virtually infinite amount of air. Given the relatively small amount of air inhaled with each breath, the probability that a breathing unit of air contains tubercle bacilli is rapidly diminishing with increasing distance from the air stream of a source case. While no precise definition can be given, we may pragmatically define that outdoors talking distance entails a measurable risk that exposure leads to infection, while being farther away does not. Outdoors, proximity between a source case and an exposed individual is thus highly relevant. In contrast, indoors the volume of air into which tubercle bacilli are expelled is finite, particularly if windows are closed and ventilation is poor. A source case may leave a room and another person entering it subsequently may become infected in that room. Physical proximity between such a person and the source case is thus largely irrelevant. It is likely that the risk of becoming infected with *M tuberculosis* in a community is importantly co-determined by the amount of time spent indoors. Climate is thus of considerable importance. |
| | 1_02 | **Survival of tubercle bacilli outdoors** <br> *1_02-1.wav*. Not only are bacilli rapidly dispersed outdoors, their survival time is also limited. Ampoules of clear glass containing BCG were exposed to open sky without direct exposure to the direct rays of the sun. The number of viable bacilli decreased from 10 million to less than 100 organisms in 10 hours. Exposed to sunlight, the same effect was achieved within 1 hour. |
| | 1_03 | **Role of general population age structure** |

| | | |
|---|---|---|
| | | *1_03-1.wav*. The population structure matters for exposure risk, as most social interactions are intra-generational with the notable exception during child-rearing. In Switzerland, for example, the percentage of households with children was halved over the past 80 years. If a household member developed tuberculosis in the 1920s, exposure risk to children was thus substantially larger than it is today. |
| | 1_04 | **Role of tuberculosis population age structure**<br>*1_04-1.wav*. The age structure of the tuberculosis patient population has changed substantially with the passage of time. The median age of tuberculosis patients shown here for Finland moved from the generation of parents to that of grandparents. This must have resulted in a large decline in the exposure risk of the youngest generation, even if the incidence of transmissible tuberculosis had remained unchanged. |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Infection | 2_00 | **Introduction to infection with *M tuberculosis*** <br> *2_00-1.wav*. In this section we recapitulate how droplets containing tubercle bacilli are produced, how they become infectious droplet nuclei, how we measure infection with *M tuberculosis* by the tuberculin skin test and how we interpret its result. We define the epidemiologic measure of infection, the annual risk of becoming infected or re-infected with *M tuberculosis* and how it differs from measuring the incidence of infection. We look how the annual risk of infection has changed in Europe over the last century and how this change has impacted on the age-specific prevalence of prior infection with *M tuberculosis*, also taking changes in the population structure into account. |
| | 2_01 | **The production of droplets** <br> *2_01-1.wav*. The risk of becoming infected is largely determined by exogenous factors. It is the product of the density of tubercle bacilli in the ambient air and the breathing exposure time to that air. <br> *2_01-2.wav*. The physical force behind a respiratory maneuver determines both the number of expelled droplets and their size. The larger the physical force, the larger the number of droplets and the smaller their size. Coughing is the most conspicuous symptom of pulmonary tuberculosis and half of the droplets expelled during a cough attack are smaller than 10 micrometers in diameter. |
| | 2_02 | **From droplets to droplet nuclei** <br> *2_02-1.wav*. The key studies to demonstrate the generation of airborne droplet nuclei were conducted by Wells at Harvard University in the USA. Two factors determine the settling tendency of droplets, the water saturation of the air and the size of expelled droplets. In unsaturated air as shown here, a considerable proportion of droplets even sized up to 100 micrometers will never reach the ground when falling from a height of 2 meters but will evaporate before they can hit the ground. Those droplets of that size which contain tubercle bacilli, measuring just a few micrometers, will evaporate to what we call droplet nuclei, essentially just infectious doses of one or more bacilli that can remain almost infinitely long suspended in the air. It is these and only these infectious droplet nuclei that play the key role in airborne transmission of *M tuberculosis*. |
| | 2_03 | **Measuring infection: the tuberculin skin test and its interpretation** <br> *2_03-1.wav*. After inhalation of tubercle bacilli and their successful invasion of the host using macrophages like a the Trojan horse, only the mounting of the cellular immune system can bring their virtually uninhibited replication to a halt. This activation of the cellular immune system leaves a long-lasting imprint that can be measured by the tuberculin skin test developed a century ago or by a more recently developed interferon-gamma release assay. If the tuberculin skin test is administered to a population, we will find a distribution of reaction sizes among the tested individuals. This distribution will be a reflection of reactions among persons with no prior infection with any *Mycobacterium* who will have an induration size of zero millimeters. This sub-group has been omitted from the display here of the results from a tuberculin skin test survey conducted in India more than 50 years ago. Those who react consist of those with a prior |

| | | |
|---|---|---|
| | | infection with *M tuberculosis* and those who had been infected with another *Mycobacterium*. The latter show generally smaller reactions than the former because of some remaining cross-reactivity to tuberculin produced from *M tuberculosis*. Cross-reactivity exists to a sufficient extent to make it difficult to determine clearly which reactions are due to prior infection with *M tuberculosis* and which are due to infection with another *Mycobacterium*.<br><br>*2_03-2.wav*. We fit here the dashed black line to the blue histogram of the observed reaction sizes in a way that accommodates the assumed two underlying distributions attributable to infection with *M tuberculosis* and cross-reactions due to other mycobacteria.<br><br>*2_03-3.wav*. The red line is the modeled underlying component distribution attributed to infection with *M tuberculosis*. Neither its normal shape nor its location are entirely arbitrary as we know from tuberculin skin test surveys among patients with tuberculosis that this is what we would expect: a distribution belonging to the family of normal distributions with a mean between 15 and 20 millimeters.<br><br>*2_03-4.wav*. The second underlying component is shown here as a green dashed line and is attributed to non-specific reactions resulting from infection with other mycobacteria. Together, these two underlying distributions add up to the black dashed line and best explain the observed distribution.<br><br>*2_03-5.wav*. In clinical practice it is common to decide on a cut-off point which separates those more likely infected with *M tuberculosis* from those more likely to be infected with another *Mycobacterium*. The cut-off point can be chosen to give preference to balancing the errors in sensitivity and specificity, favoring sensitivity, or favoring specificity. In the example of the cut-off point here, preference is given to sensitivity: very few people with infection attributable to *M tuberculosis* are excluded, shown with the red letter "c", thus "a" out of all infected, denoted as "a plus c", is a large proportion. Conversely, the number falsely included, denoted with the green letter "b", contribute importantly to all who are not infected with *M tuberculosis*, thus specificity at this cut-off point is relatively poor.<br><br>*2_03-6.wav*. Depending on the purpose of testing in clinical practice, the cut-off point is modified: moving it to the right increases specificity at the cost of loss in sensitivity, moving it to the left does the opposite: one cannot have it both ways. In individual medicine, cut-off points are desirable to make the choice of preference for instance between trying to miss as few as possible who might benefit from preventive therapy or to prevent prescribing preventive therapy to persons who are not at risk of tuberculosis. In epidemiologic studies at the population level the objective is not for a given preference but for balancing the two respective errors as good as possible to arrive at an as correct as possible estimate of the prevalence of prior infection with *M tuberculosis*. |
| | 2_04 | **The indicator: annual risk of infection with *M tuberculosis***<br><br>*2_04-1.wav*. For various technical and logistic reasons, it is not practically possible to measure the incidence of infection with *M tuberculosis* in a population. To do so would require serial testing of large numbers of people at short intervals such as one year. We thus approximate the incidence of infection by calculating an average annual risk of infection with *M tuberculosis* from the prevalence of infection derived from a tuberculin skin test prevalence survey. How we do this algebraically is shown in this slide. People are born free of infection with *M tuberculosis*. If we assume the risk "R" of becoming infected |

| | | |
|---|---|---|
| | | during the course of one year, then the probability of remaining uninfected at the first birthday is "1-R". If this risk remains the same during the second year of life, the probability of remaining uninfected is "1-R squared". For example, if we take "R" to be 10 per cent, 90 per cent remain uninfected at the first birth date, and 81 per cent at the second, and so on. As we know the age of the population in which we make a tuberculin skin test prevalence survey, we can calculate the average annual risk of becoming infected or re-infected that was necessary to accumulate the observed prevalence of infection. |
| | 2_05 | **Incidence vs risk of infection with *M tuberculosis***<br><br>*2_05-1.wav*. The thus calculated risk is aptly termed "the average annual risk of infection with *M tuberculosis*". The same prevalence could be observed if the actual incidence of infection had declined, increased, or indeed had taken more complex shapes. At some point in time between the birth of the cohort enrolled in the survey and the time of the survey the calculated risk of infection was exactly the same as the actual incidence. It is likely to lie at some point in time between birth and prevalence survey year. When exactly can be determined only by serial surveys. Failing such, the average annual risk is commonly and best approximated to lie in the middle between birth and survey time. |
| | 2_06 | **Risk of infection with *M tuberculosis* and trend in Europe**<br><br>*2_06-1.wav*. Several countries in Europe have conducted serial tuberculin skin test surveys during the last century and from these it is possible to derive the trend in the annual risk of becoming infected with *M tuberculosis*. There is a substantial body of data that suggests that the annual risk of infection was in the order of 10 and more per cent in western Europe at the beginning of the 20$^{th}$ century, a magnitude that is unlikely to exist nowadays in any country in the world although in some sub-populations studied in South Africa it may be currently as high as 5 to 7 per cent. Notably, the risk of infection with *M tuberculosis* in western Europe declined annually by around 4 per cent up to around the time when chemotherapy was introduced, then the annual decline accelerated after the second World War to 10 to 12 per cent per year. It is remarkable to note that the speed of decline in the latter part of the last century was virtually the same in all countries with such survey information. Currently, the annual risk of becoming infected has declined to between 10 and 100 infections per year and one hundred thousand population. |
| | 2_07 | **Prevalence of infection with *M tuberculosis* in Switzerland**<br><br>*2_07-1.wav*. The huge annual risk of infection, its continuous decline, and the aging of the population have had a tremendous impact on the remaining prevalence of prior infection with *M tuberculosis* as exemplified here for Switzerland. In 1900, some 12 per cent of the Swiss population were children under the age of 5 years and one third of them, shown as the red hatched area in the graph, had already become infected with *M tuberculosis*. The decline in the infection risk affected the children first, and only gradually did it also impact on the older population segments who had been born when the risk was high and thus carried this history with them as they were aging. Only late in the passage of time does the impact of the decline also make its imprint on the oldest generation. These events have all important repercussions on observed tuberculosis incidence over time and cross-sectionally as tuberculosis can only emerge among persons who have ever become infected with *M tuberculosis*. |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Tuberculosis | 3_00 | **Introduction to tuberculosis**<br>*3_00-1.wav*. In this section, we will look at some important risk factors for developing tuberculosis following infection and then proceed to describe the course of the tuberculosis epidemic in western Europe over time. |
| | 3_01 | **Risk of tuberculosis given infection by time elapsed since infection**<br>*3_01-2.wav*. The risk of progression from infection with *M tuberculosis* to clinically overt tuberculosis is largest in the immediate period subsequent to acquisition of infection and drops from about 1 per cent to 1 per 1,000 in the first 5 to 10 years. This is demonstrated here in two placebo-recipient cohorts in clinical trials with a prolonged follow-up. Depending on the age at infection, the risk of tuberculosis immediately following infection may vary importantly. |
| | 3_02 | **Lifetime risk of tuberculosis**<br>*3_02-1.wav*. It is not practically possible to measure the actual cumulative lifetime risk of tuberculosis and modeling techniques must be applied to existing data as was done here for England and Wales over a time span of 90 years. The authors arrived here at an estimate of an approximately 10 per cent lifetime risk, an estimate that is similar to that arrived at in other settings. |
| | 3_03 | **Age as a modifier of tuberculosis risk given infection**<br>*3_03-1*.wav. The risk of progression from infection to tuberculosis varies greatly at different ages. While it is notoriously difficult to separate maturation factors from time elapsed since infection, it is commonly agreed that the risk is highest in infancy, dropping sharply until primary school age, and increasing again with onset of puberty to reach a second maximum among young adults and then decreases again to reach relative low levels from about 25 years onwards. |
| | 3_04 | **Sex as a modifier of tuberculosis risk given infection**<br>*3_04-1.wav*. The risk of becoming infected and the resulting cumulative prevalence of infection with *M tuberculosis* is commonly larger among males than females of the same age. The largest risk of becoming infected ever recorded in history has been in Alaska in the 1940s with some 25% annually. In such a setting, the force of transmission is so large that it will affect both sexes to a very similar extent. It is in such settings where any difference in the risk of progression to tuberculosis between the sexes can be studied most accurately.<br>*3_04-2.wav*. Such an analysis of the Alaska data shows that the risk of tuberculosis given infection among young adults is larger for women than for men, a finding that has been confirmed in other settings, for instance in Denmark and other European countries. With increasing age, the risk becomes more similar among the two sexes. |
| | 3_05 | **Sterilization of primary infection**<br>*3_05-1.wav*. It is a widely but most likely inappropriately held opinion that once infection with *M tuberculosis* has been acquired, it will persist for the rest of every individual's lifespan. A number of studies in the 1930s examined specimens obtained at autopsy from individuals with pathological evidence of |

| | | |
|---|---|---|
| | | prior tuberculosis and it was noted that the vast majority of primary lesions was sterile. While this does not prove that bacilli could not be hiding alive in other tissues, it is nevertheless a very strong indication that perhaps a large proportion of persons who have become infected with *M tuberculosis* will ultimately eliminate the organisms. |
| | 3_06 | **Role of exogenous infection in pathology**<br><br>*3_06-1.wav*. In the same period, it was also noted that many individuals had clear evidence of multiple lesions resulting from repeat re-infections. |
| | 3_07 | **Primary, endogenous reactivation, and exogenous re-infection tuberculosis**<br><br>*3_07-1.wav*. In extension of pathological findings, epidemiologic definitions were sought to determine contributors to overall morbidity. We follow here the definitions that were proposed by Holms and later refined by Sutherland. The first criterion is a cut-off point for time elapsed since infection. Five years were chosen, derived from the observation of the decline in the risk to a steady low level in about this time period following infection. Tuberculosis is then defined to be either "primary" below, or "endogenous reactivation" tuberculosis above the cut-off point, if it is resulting from a single infection. If the person has been infected more than once and at least one of these re-infections had been acquired 5 or more years after the first, then it was defined as "exogenous re-infection tuberculosis".<br><br>*3_07-2.wav*. This concept was applied statistically to data from the Netherlands. What is shown here is modeled, but the evidence for the correctness of the concept is emerging now with the availability of molecular epidemiology. If tuberculosis is found in a young person, it is intuitively suggestive that it is most likely the result of a progression from a single infection acquired in the past five years. Nevertheless, in the 1950s the risk of becoming infected was still high in the Netherlands and a certain proportion of patients in this age group may had acquired more than one infection and developed tuberculosis now at this age. Some might also had a single infection but which had been acquired longer than 5 years ago. With the steep decline in the annual risk of becoming infected, the proportion with primary tuberculosis at this age was bound to increase, while almost mirroring it, the risk of exogenous re-infection tuberculosis was declining.<br><br>*3_07-3.wav*. Quite in contrast, if one examines elderly patients, it must have been extraordinarily unlikely in 1950 for a person born when the risk of becoming infected had been in excess of 10 per cent to have now tuberculosis as a result of a single and first infection acquired just in the previous five years, a time by when the risk of infection had already substantially declined. Primary tuberculosis at that age must thus have been a small contributor to overall observed tuberculosis morbidity, while the likelihood of "exogenous tuberculosis" must have been the major contributor. Over the ensuing 20 years, the risk of becoming infected with *M tuberculosis* decreased to a quarter of the value in 1950 and the probability of "exogenous tuberculosis" in 1970 had thus substantially declined while the role of "endogenous tuberculosis" became much more prominent. This statistical exercise shows conceptually that the proportions of the three contributing components depend critically on both the current risk of infection or re-infection and the age in which tuberculosis occurs. |
| | 3_08 | **HIV infection as a contributor to morbidity**<br><br>*3_08-1.wav*. HIV infection is the strongest ever identified risk factor for progression of latent infection to tuberculosis and over the past 25 years it has |

| | | |
|---|---|---|
| | | emerged as a driving force of a deteriorating tuberculosis situation in many sub-Saharan countries. Irrespective of the setting, a person with dual untreated infection has a huge tuberculosis risk. Depending on the stage of HIV infection it is between 5 and 15 per cent per year rather than cumulatively in a lifetime.<br><br>*3_08-2.wav*. The impact at the population level depends on the size of the HIV incidence and prevalence and the incidence and prevalence of infection with *M tuberculosis* in a community, but most critically on the extent to which these two respective infection prevalences overlap. In the previous section we have shown how first incidence and then prevalence of infection with *M tuberculosis* diminished and virtually disappeared from young adults in Switzerland. HIV-associated tuberculosis has thus had only a marginal impact on the epidemiology of tuberculosis in most of western Europe. This is quite in contrast to the situation in sub-Saharan Africa.<br><br>*3_08-3.wav*. HIV impacts in three possible ways on the tuberculosis epidemiology, two are the direct result, and one is an indirect consequence. The direct effects depend on the sequence of acquisition of the two infections, thus both occur among HIV infected patients. Excess cases are thus produced as a direct effect of HIV infection, cases that would not have occurred without it. Whichever the sequence, these excess cases can transmit *M tuberculosis* to the population not infected with HIV and result there in secondary cases that would also not have occurred without the HIV epidemic. The latter we call with Sutherland the indirect effect.<br><br>3_08-4.wav. These three effects are demonstrated in this case report from a nosocomial outbreak in an HIV clinic in Italy. A hospitalized HIV infected patient developed unrecognized tuberculosis in a ward. Quite likely this was the first mechanism with pre-existing latent infection with *M tuberculosis* that progressed to tuberculosis with declining immunity as a result of superimposed HIV infection. Within less than two months, 6 HIV infected patients in the same ward developed tuberculosis, most likely as a result of the second mechanism, having pre-existing HIV infection and now acquiring super-imposed infection with *M tuberculosis* that could not be contained and progressed directly to tuberculosis. Six months later a health care worker exposed to these patients developed tuberculosis, most likely reflecting the third mechanism, having become infected by any of the 7 HIV-infected patients while not having HIV infection him- or herself. If this happens in the hospital setting, this will also happen in the community, although the actual contributing fractions cannot easily be determined in a given community. |
| | 3_09 | **Quality epidemiological surveillance**<br><br>*3_09-1.wav*. To be informed about the magnitude and particularly the time trends in tuberculosis incidence, a high-quality surveillance system is indispensable. The surveillance system in the United States is exemplary for its quality. It has a two-pronged approach. The first element is a simple and sensitive report of weekly case counts by each jurisdiction in the country, compiled to weekly reports at the national Centers for Disease Control and Prevention. The emphasis in this system is on sensitivity and timeliness. The second pillar uses a specific and more elaborate report of each verified case of tuberculosis where timeliness is less paramount than accuracy, and more epidemiologically detailed information is required. It was the first simple case count that was used here to compare the change in the cumulative weekly case count in 1984 with that of the same reporting week in 1983. With the cumulatively growing number through the year, the change is stabilizing |

| | | |
|---|---|---|
| | | towards about the middle of the year and allows already at that time to observe that the decline from the previous year was about 8 to 10 per cent, quite as expected from the earlier years.<br><br>*3_09-2.wav*. The same method of comparison was used in 1985, where by middle of the year it became apparent that something was going wrong. By the end of the third quarter it was irrefutably clear that tuberculosis failed to decline as expected and the American public was promptly alerted to this observation in early October 1985 and the hypothesis formulated that HIV infection may be co-responsible, a hypothesis later confirmed in more specific investigations. It was also the first ever national report to point at the impact HIV infection may have in store on the epidemiology of tuberculosis. The key message is that quality of surveillance is essential to interpret and act upon changes, and that this is best achieved by limiting it in a first and top priority to an impeccable case count. |
| | 3_10 | **Sex ratio over time**<br><br>*3_10-1.wav*. Sex differences in the prevalence of infection with *M tuberculosis*, and risk of disease progression given infection have been discussed earlier. The notification data from Denmark show a regular increase in the ratio of male to female case notification rates of incident cases over a forty-year period from considerably less to considerably more than one. The most likely epidemiologic explanation is related to the decline in the risk of becoming infected with *M tuberculosis*, the resulting shift in the prevalence of infection to older age groups and thus the emergence of cases, coupled to the age-specific sex differences in progression from infection to tuberculosis. In 1900 the risk of becoming infected was very large in Denmark, and thus by 1920, the prevalence of infection was about 80 to 90 per cent at age 20. With such a high force of transmission, differences in the prevalence of infection between males and females are by necessity relatively small and as the risk of progression to tuberculosis is highest at this age and is also much larger among females than among males, it is not surprising that in 1920 overall case rates were much higher among women than among men. Over time, the risk of becoming infected decreased in the population, the prevalence of infection was gradually reduced among young adults, and male-female differences in the infection prevalence may also became larger, disfavoring males. As infected women of older age are no more that disadvantaged in their risk of progression if infected compared to males of the same age, the change in the sex ratio of cases becomes gradually and distinctly observable. This change accompanies the overall decline in tuberculosis morbidity and results in a shift in the age structure of the tuberculosis patient population as demonstrated at the beginning with the example from Finland. |
| | 3_11 | **Contrasting morbidity in two countries**<br><br>*3_11-1.wav*. In the 40-year period from 1940 to 1980, tuberculosis notification rates in Switzerland declined by about 80 per cent. While the case definitions and the surveillance systems are not strictly comparable, we note that the notification rates in Tanzania were at about the level Switzerland reported in the 1950s. There was thus justified hope that the then newly established national tuberculosis program in Tanzania with a secure supply of anti-tuberculosis drugs could manage to achieve at least a somewhat more modest decline in morbidity, to perhaps halving the problem in a generation.<br><br>*3_11-2.wav*. These expectations for an improving situation were apparently premature as the HIV epidemic hit the country in full force in a population |

| | | |
|---|---|---|
| | | segment which had perhaps some 30 to 50% per cent prevalent, prior acquired infection with *M tuberculosis*. While in Switzerland tuberculosis continued to decline exponentially, it increased mirror-like exponentially in Tanzania, tripling over the span of a generation. |
| | 3_12 | **Tuberculosis among the foreign-born**<br><br>*3_12-1.wav*. Like in many other countries of western Europe, tuberculosis has declined in Denmark almost exponentially among the population born in the country, with a reduction in the number of cases of about 75 per cent in 25 years.<br><br>*3_12-2.wav*. While tuberculosis among the indigenous population is disappearing, Denmark, also like most countries in western Europe, has immigration with a changing provenance of immigrants, increasingly also originating from countries with a higher tuberculosis incidence. Since the mid-nineties, more than half of notified incident cases are reported among the foreign-born. Tuberculosis will thus not disappear from western Europe in the foreseeable future. |
| | 3_13 | **Morbidity cross-sectionally and by birth cohort**<br><br>*3_13-1.wav*. From what we know about the change in the underlying prevalence of infection with *M tuberculosis*, we expect to see a decline in tuberculosis incidence over time. We also expect tuberculosis incidence to peak at early adulthood in the earlier period and then observe a gradual shift of the peak to a higher age as is documented here in an analysis of data from Finland by Härö. Looking cross-sectionally at age-specific morbidity in a given year is the usual way to look at data. In 1930, a Norwegian, Kristian Andvord demonstrated that a cross-sectional analysis alone fails to tell the whole story. If sufficiently detailed data are available, it is possible to also look at the epidemiology of tuberculosis within birth cohorts. Applying this to the data from Finland, we can readily note that patients aged 70 to 74 years in 1994 were born in the year 1922. The same birth cohort was ten years younger in 1984 and we can connect the two points to show the experience by the 1922 birth cohort in this decade.<br><br>*3_14-2.wav*. We extend now with Härö the line of the birth cohorts as far back in age as we can and add the corresponding lines for all birth cohorts for which data are available. What emerges is an entirely different picture. It clearly shows that morbidity in each birth cohort peaked among the 20- to 24-year-old. What we now see cross-sectionally as tuberculosis peaking at an old age is just a residual of an even higher morbidity each birth cohort experienced when it was young and their infection had been acquired more recently. This is one of the factors contributing to the higher morbidity at a young age. The other we have seen is that the risk of tuberculosis given infection is also highest in that age group. These observations fit thus well with the decline in the risk of becoming infected over time with a shift in the remaining prevalence towards higher age groups, what we know about the risk of progression given infection given recently versus remotely acquired infection, and the age as an important modifier. |
| | 3_14 | **Projecting tuberculosis from birth cohorts**<br><br>*3_14-1.wav*. Härö extends his analysis further and takes the observations of the experience by birth cohort, shown by the black lines, and makes a fairly simple extrapolation of these into the future, shown by the blue hashed lines. Then he reverts the process back and constructs the lines of what he predicts as |

| | | |
|---|---|---|
| | | expectations for the cross-sectional incidence rates for the years 2000 and 2010. Now anybody can make predictions, but do they hold?<br><br>*3_14-2.wav*. Actual notification rates were available for the year 2000 and the accuracy of the prediction is remarkable. One may note that even the shape of the observed among those aged 50 years and older is exactly in parallel with the predicted. Finland is in many ways exceptional in that it has little immigration. It has also not experienced any important impact from other newly arising influences such as HIV infection. Within these constraints, it is teaching us that tuberculosis does not behave haphazardly but follows a very predictable path that is shaped by the underlying change in the risk of becoming and being infected with *M tuberculosis* from which incident cases will emerge. |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Death | 4_00 | **Introduction to death from tuberculosis**<br>*4_00-1.wav*. The final in the chain of events we have discussed is death from tuberculosis. We will first examine case fatality in the pre-chemotherapy era, then turn to mortality how it developed in Europe over time and conclude with an observation how chemotherapy affected fatality as reflected in mortality at the population level. |
| | 4_01 | **Fatality of untreated tuberculosis, by microscopy**<br>*4_01-1.wav*. In the pre-chemotherapy era, case fatality was importantly determined by the result of sputum examination as this long-term follow-up of sanatorium patients shows. As cultures were not routinely available at that time, "open" is largely synonymous with "sputum smear-positive". For such patients, the cumulative risk of death reached 70 per cent after 5 years. |
| | 4_02 | **Cumulative fatality in three European countries**<br>*4_02-1.wav*. Similar case fatalities have been documented in other settings in western Europe, as exemplified here by three studies from the United Kingdom, Sweden, and Denmark, ranging from 65 to 85 per cent after 10 years. |
| | 4_03 | **Mortality in three European cities**<br>*4_03-1.wav*. Despite the limitations in diagnostic accuracy, this compilation of mortality data by Grigg suggests that annual mortality from tuberculosis was as high as 1 per cent in London around the year 1750. On the continent, peak mortality was reached later, the shift on the time axis reflecting industrialization which came first about in the United Kingdom. The graph shows the continuous decline despite the fact that no medical intervention was available. The sanatorium movement started around 1870 but did seemingly not accelerate the decline. Effective triple chemotherapy became available only after the timeline of this graph ends. |
| | 4_04 | **Morbidity-to-mortality ratio**<br>*4_04-1.wav*. Half of all tuberculosis patients died before the advent of chemotherapy but fatality was reduced to a quarter, then to 20 percent after its ever wider availability as documented here with data from Denmark. |
| | 4_05 | **Mortality from tuberculosis cross-sectionally and by birth cohort, males**<br>*4_05-1.wav*. Similar to morbidity, we look now at mortality first cross-sectionally then by birth cohort, here for males in Switzerland. Cross-sectionally, we observe the decline over time and a peak among the elderly. By birth cohort, we find that in every cohort death rates were highest among young adults, the observed cross-sectional peak among the elderly merely reflecting an even higher mortality each cohort experienced when it was young, a phenomenon consistently seen where tuberculosis has been in decline for a long time.<br>*4_05-2*.wav. We introduce one additional way to look at the same data. If we display the data on a linear scale, we would be hard pressed to decide which age group experienced the largest decline from group 1 (which are the actual 1901 data) to group 2 (a made-up later point in time). In absolute terms, the largest |

| | | |
|---|---|---|
| | | decline is clearly among the 60- to 69-year-old, but for a comparative purpose we are often interested in a relative change.<br><br>*4_05-3.wav*. A logarithmic display of the same data shows that the relative decline is identical across all age groups as evidenced by the parallelism of the two lines.<br><br>*4_05-4.wav*. Showing the mortality by birth cohort on a logarithmic scale, the lines are more or less parallel through the 1906 birth cohort, suggesting a regular relative decline across all age groups. A first conspicuous deviation is observed from the 1906 to the 1916 birth cohort and the red arrow points at those aged 45 years of age. It is in 1961 that this birth cohort was 45 years old, a year by which effective triple-chemotherapy had become universally available in Switzerland. In the same year, the 1926 birth cohort was 35 years old and the 1936 birth cohort 25 years old. For the latter cohort, we note that chemotherapy had virtually cut off the former peak in mortality at this age: tuberculosis had lost its threat as a death sentence for young adults. |
| | 4_06 | **Mortality from tuberculosis cross-sectionally and by birth cohort, females**<br><br>*4_06-1.wav*. We show here the same approach for females, first cross-sectionally, then by birth cohort on a linear scale, and finally by birth cohort on a logarithmic scale. Notable is the difference to males in the age-specific mortality. Among females, even cross-sectionally the peak among young adults is clear. This is explained earlier by the observation that at a young adult age, women given infection have a higher tuberculosis risk than men of the same age, and thus mortality follows, while among the elderly, this is not the case. By birth cohort, the differences in mortality by age are thus even more pronounced. The effect of chemotherapy was thus relatively even greater among women than among men.<br><br>With this encouraging note we have reached the end of this presentation of the epidemiology of tuberculosis in western Europe over the past century. |

| Section | HTML name | Clip description and narrative |
|---|---|---|
| Summary | 5_00 | **Summary**<br><br>*5_00-1.wav*. This concludes the presentation on the dynamics of the tuberculosis epidemic in western Europe, from which more generic lessons might be gleamed.<br><br>The intent was to provide some insight into the key role of exposure to *M tuberculosis* and subsequent infection, how the latter impacts on current and future morbidity, and in last consequence on mortality.<br><br>The reasons for the decline of tuberculosis remain largely elusive. They are least likely attributable to medical interventions. The latter, however, had a profound impact on mortality when chemotherapy became available for the entire population. It cut off the peak of mortality among young adults, among whom, before it became available, a diagnosis of tuberculosis had virtually been a death sentence.<br><br>Progress in tuberculosis control and a move towards elimination is slow as this presentation spanning more than a century shows.<br><br>Barring a vaccine that is highly effective in preventing progression from latent infection with *M tuberculosis*, the fact that tubercle bacilli can hide in a human host for decades will always remain a barrier to a quick solution. |
| | | |