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0_01 This presentation will delineate the secular course of the tuberculosis epidemic in a community. The presentation is based on data from Western Europe. It spans a period of more than one century. The purpose is to provide epidemiologic information that gives insight into the dynamic of tuberculosis in a population and should thereby open an understanding on how interventions might best be invoked. However, the discussion of interventions is not subject of this presentation.

0_02 To facilitate the understanding of tuberculosis epidemiology, the tuberculosis classification of the American Thoracic Society can serve as useful model. It follows the pathogenesis of tuberculosis with exposure, latent infection, tuberculosis the disease, and death from tuberculosis.

Risk factors determine the conditional probability of progression from one to the next step in this sequence.

1_00 We will go sequentially through each of these steps, starting with exposure to tubercle bacilli. *Mycobacterium tuberculosis* is transmitted by the airborne route from one to another individual. Thus, there must be sources of transmission in the community whom an individual must have an opportunity to get exposed to.

1_01 How do we define exposure? As we cannot measure exposure, we might pragmatically define that "relevant" exposure is one that leads to a measurable chance of actually getting infected with *M tuberculosis*. In other words, the person exposed to tubercle bacilli in the ambient air actually inhales tubercle bacilli, so that they lodge in the lungs of that individual. As we all share the same air, we are all potentially exposed to air containing tubercle bacilli, but it is apparent that not all such exposure is relevant. Outdoors, for instance, proximity to a source shedding bacilli into the air must likely be physically close, else the expelled bacilli are rapidly dispersed in a virtually infinite amount of air that makes the probability of inhaling even one bacillus for any other individual unmeasurably small. Pragmatically then, outdoors, relevant exposure may occur if a source expelling tubercle bacilli is in talking distance to another individual. In contrast, indoors proximity is much less relevant as tubercle bacilli may be trapped in a virtually finite amount of air if windows are closed. Indeed, physical proximity is not even necessary indoors as a person with tuberculosis could have expelled bacilli into the air and have left the room before another person entered that room still containing tubercle in the ambient air that then might be inhaled.

1_02 Outdoors, tubercle bacilli are not only rapidly disbursed, but they are also sensitive to ultraviolet light killing them rapidly as shown here, not just in bright sunlight, but even on an overshadowed day.

1_03 To get an understanding of the dynamics of tuberculosis in a population, it is also important to know something about the demographic changes that have occurred in that population. In Switzerland and other industrialized countries, a conspicuous change has been the change in family size. Over an 80-period of time, the number of children counted at any point in time in a household has almost halved.

ch_pop Here we look at the population structure by 1-year age groups in Switzerland and follow this annually over the 110 years from 1900 to 2009. We note that in 1900, about 2.5% of the entire population was below 1 year old, in 2009, it was only 1%. On the other hand, life expectancy increased substantially and as a result, the proportion of persons aged 65 years or older increased from 3% in 1900 to 17% in 2009.

1_04 From the population age structure we turn our look now at the change in the age structure of the tuberculosis patients. In Finland, the median age of tuberculosis patients has changed from about 35 years in the 1950s to around 60 years in the 1990s. Does this have an influence on exposure risk in the community? Importantly so: if tuberculosis moves from the generation of parents to that of grandparents, then exposure risk of the youngest children must have substantially changed in this population in which it is the parents rather than the grandparents who spend most of the time with the children. In other societies this may differ, but the age at which tuberculosis occurs will always have a substantial impact on who is getting exposed.

2_00 Now that we have an understanding of what contributes to exposure risk, we turn to latent infection with *M. tuberculosis*. Persons who are exposed to tubercle bacilli may inhale one or more bacilli possibly leading to infection with *M tuberculosis*, i.e. harboring live bacilli in the lungs. In this section we will examine how tubercle bacilli reach the ambient air and characteristics that makes them capable of reaching the lungs of an exposed person. We will provide information on how we measure transmission of *M tuberculosis* in the community and how that risk of infection has changed in the course of time and how it has affected who in the population has ever become infected over their life time.

2_01 The risk of becoming infected is largely exogenous in nature, i.e. whether one gets infected or not depends solely on whether tubercle are inhaled or not. The chances of inhaling tubercle bacilli depend on the concentration of the bacilli in the ambient air and the duration of inhaling that air. Our tidal volume of inspiration is approximately 500 mL. Thus, if the surrounding air contains 1 bacillus per 1 L air, then on average an individual needs two breaths to inhale one bacillus.

Whether bacilli are expelled into the air from an individual with tuberculosis depends on the site of tuberculosis: for all practical purposes, the site of tuberculosis must be the respiratory tract and more specifically and most prominently the lung parenchyma. The physical force behind a respiratory manoeuver will determine both the number and the size of the droplets an individual produces. Breathing has the least physical force, talking is a stronger force, then comes coughing, and the strongest force of all is sneezing. However, sneezing is a symptom of upper respiratory tract infections. It is largely irrelevant in tuberculosis where severe, disabling cough is a most prominent sign and symptom. This graph shows that half of the droplets produced by coughing are small-sized with 10 or fewer micrometers in diameter, while only about 10% of those produced by talking are of that size.

2_02 The size of expelled droplets determines whether they fall quickly to the ground, here shown from a level of 2 meters approximating the level of our mouth or whether they remain longer suspended in the air where evaporation of the liquid diminishes their aerodynamic diameter further. Small droplets containing one or more tubercle bacilli may then evaporate all liquid so that only the bacilli (which have a length of about 3 to 5 and a thickness of about 0.5 micrometers) remain suspended in the air for a very long time, floating where the air current carries them. These are called droplet nuclei and its these which are relevant for transmission. If we inhale large particles they will adhere to the bronchial system as they cannot reach the alveoli in the periphery of the lung and infection will rarely take place from here. The

probability to reach an alveolus rapidly increases with particle diameters below 10 to 12 micrometers. Particles might be optimally sized with around 3 to 7 micrometers. Particles of that size reach an alveolus, attach to it and are recognized by alveolar macrophages which engulf them and transport them into the lung tissue. *M tuberculosis* has the ability to usually prevent the fusion of the lysosome and the phagosome and thus its own digestion, retaining thus reproducibility and ability to establish latent infection.

2_06 We can measure latent infection, or more precisely, determine the prevalence of immunologic leftovers from a prior infection with tubercle bacilli that triggered an immunologic response. The longest available is the tuberculin skin test. More recently the interferon-gamma release assay has been introduced. An infection with tubercle bacilli induces a cell-mediated immune response through effector cells which is long-lived but not for a life time like that related to central immunity as we know from immunity induced by infections like smallpox virus. If we place a tuberculin skin test in an individual, we thus measure a large part of the accumulated lifetime experience in acquired infection with *M tuberculosis*. Epidemiologically speaking, we measure the prevalence of infection. By definition, prevalence accumulates with age. If we wish to compare the experience with *M tuberculosis* infection in two population groups, we thus need some standardized approach. We can algebraically derive the so-called annual risk of infection from the measured prevalence if we know the age of the survey population. It is the annual average probability to have become infected between birth and the time of the prevalence survey. It is thus an approximation of the average incidence of infection. As it is an average and does not take changes in risk over the lifespan nor in the age at the point of infection into account, it is displayed commonly at the midpoint between the calendar time of birth and that of the survey in the individual. If two surveys are available then the line connecting the calculated risk of infection at the two calendar times gives the trend. For the countries shown here, multiple surveys at different calendar times were available, so this was converted into series of annual risks of infection. The scale is semi-logarithmic, and the slope reference shows the shape for different annual percentage declines. The data suggest that the annual chance of becoming infected during the course of one year was in the order of 10% at the beginning of the 20th century. It declined annually by up to 5% even before the introduction of chemotherapy and subsequently the average annual decline accelerated to 10%-15% until already by the 1990s it became barely measurable anymore in the Netherlands for instance. While it seems than France and Norway lag behind the Netherlands by a decade or so, on the large time scale that the tuberculosis epidemic runs, this matters actually little.

ch_pop_inf: We have seen earlier the change in the population structure. In this changing population, we now add the change in the risk of infection at the same calendar time and the resulting effect on the accumulated prevalence of infection. We make thus back-calculation modeling: we derive the annual risk of infection from measured prevalence of infection, then apply this risk to the population, assuming that in a given calendar year it was the same among both sexes and at all ages (an over-simplification) and get thus a calculated prevalence of infection at each year of age in a given calendar year. For instance, if the risk of infection is 10% in the first year of life, and 2.5% of the population are below 1 year of age (the situation in around 1900), then 0.25% of the entire population is infected and below 1 year of age. In the second year of life, the prevalence is the sum of the prevalence this cohort experienced in their first year of life plus the incidence experienced during the second year of life which is also 10% as it is in the same calendar year. We thus calculate it for each year of life in a given calendar year and then go to the next calendar year with a slightly different population age structure and a slightly changed annual risk of infection. What we see over the 110 years shown here is how in the early years, a very large proportion of the young adult population

was infected and that with the rapidly changing risk of infection the risk for young persons to become infected declined and together with the population change, the prevalence of infection moved out from the young to the elderly. Indeed, a person aged 100 years in 2009 was born in 1909 when the risk of infection with *M tuberculosis* in Switzerland was still around 10%. This person was thus at high risk of becoming infected by young adulthood, and despite the decline in risk of infection, the long life lived provided further opportunity to become infected at some point in time. Not all people shown here colored as the brownish segment still carry live bacilli, but they are those who had once become infected and future tuberculosis can only develop among such persons: no cases can ever emanate from the never infected population segment left green here. This cohort effect also shows that the risk of infection has been declining so substantially and regularly among the Swiss (and likely other western European populations) that it is very unlikely that anything can stop the virtual self-elimination of latent tuberculous infection in the indigenous population simply by the cohort effect: infected older population segments die and are replaced by birth cohorts with an increasingly smaller risk of becoming infected themselves.

3_01 The key to the understanding of the epidemiology of tuberculosis is understanding latent infection shown in the previous block of clips. Moving now to the tuberculosis (the manifest disease), the first question we may ask is how large the risk of progression from latent infection with *M tuberculosis* to overt clinical tuberculosis actually is. Most infectious diseases have a finite, well defined incubation period. That is, the interval between acquisition of the microorganism and the clinical manifestation of the disease is well characterized. For instance, the maximum incubation period for poliomyelitis is just over one month. In other words, it is impossible to develop polio two months after ingesting the polio virus. This is not so at all in tuberculosis. A person may develop tuberculosis within weeks, months, years or even after decades after infection with *M tuberculosis*. This slide shows the long-term follow-up of persons not receiving any intervention in two different trials with remarkably similar observations. The risk of developing tuberculosis is largest in the first year following infection with the bacilli, then it drops rapidly to an annual risk of about 1 per 1,000 and then hovers there around for the rest of the observation period of up to 20 years. If we add it all up, the cumulative life time risk is in the order of 10% for a young person (but not a small child for whom it is larger). This is, if no other risk factor is known that increases the risk of progression.

3_02 The life-time risk has been estimated in this model with data in England and Wales and the authors also arrive at an approximately 10% to 15% life-time risk for pulmonary tuberculosis.

3_03 The risk of progression varies greatly with age. Small children in whom the cellular immune system is not yet fully matured, have a very high risk of progression to manifest tuberculosis if they become infected. The risk of progression appears to be smallest in primary school years then increases again in puberty to a second peak in young adults.

3_04 Of the epidemiologically two most important variables, we have examined age. In this clip, we try to disentangle the role of biological sex on tuberculosis risk. This is more difficult than it may appear at first sight. We have seen earlier that the risk is highest shortly after infection. Not shown was that the risk of infection is similar between boys and girls. After puberty, the risk of becoming infected is commonly higher among males than among females. Thus, if we compare 100 infected females and males aged 20 years, then the males will contain a higher proportion of recently infected persons than the females, thus we would see that males have a higher risk of tuberculosis than females. Yet, it is not the sex that makes the difference, but the different underlying frequency of recent infection. To control for this confounding factor, we have to look for a situation where the influence of recent infection is not importantly

different among the two sexes. Alaska had historically the highest ever recorded risk of infection. The force of infection here was such that by age 15, about 90% of both boys and girls were already infected. Thus, to become infected it didn't really matter whether a person was male or female.

It is thus permissible to look at a male-to-female ratio adjusted for underlying tuberculous infection and we note that from about age 15 to 40 years that ratio is always below 1. In other words, in this age bracket, *M tuberculosis*-infected females have higher rates of tuberculosis than infected males of the same age. Similar in principle observations can be made in some other countries and it is likely generalizable that among young adults infected with *M tuberculosis*, females are at greater risk of progression from latent infection to tuberculosis then males.

3_08 The strongest risk factor yet identified as increasing the baseline risk of progression of latent infection to overt clinical tuberculosis is HIV infection. There are multiple studies that testify to this. Here a selection of only three studies is shown. Earlier we saw that the life-time risk was in the order of 10%, here among HIV-infected persons it is the annual risk that is in this order of magnitude. The variation here apparent is dependent on and perhaps best explained by the stage of HIV Infection at recruitment into the study.

How much HIV-associated tuberculosis one may observe in a population depends on the size of the two population segments infected with *M tuberculosis* and HIV respectively, and how much the two overlap. For instance, in many industrialized countries the *M tuberculosis*-infected population segment is now old while HIV infection is mainly found in younger adult population segments. In contrast, in sub-Saharan Africa, the two respective segments share the age characteristic.

There are three ways how HIV may impact on tuberculosis epidemiology, two are direct, and one is direct. HIV infection might be superimposed on pre-existing infection with *M tuberculosis*, or it precedes it. These two sequences directly modify and increase the risk of developing tuberculosis from latent infection. Among cases thus emerging will be excess cases capable of transmitting *M tuberculosis* to the population not infected with HIV and not yet infected with *M tuberculosis*. To some extent, these newly infected persons will develop tuberculosis themselves and thus reflect the indirect impact of HIV infection on tuberculosis epidemiology.

This can be shown anecdotally in an example from a nosocomial outbreak of tuberculosis before the advent of anti-retroviral therapy. An HIV-infected index patient was admitted to a ward with other HIV-infected patients and developed tuberculosis without being immediately diagnosed as such. Within two months 6 co-hospitalized HIV-infected patients developed tuberculosis, and one health care worker developed tuberculosis 6 months after the index case. It can be hypothesized (but not proven) that the first patient followed the above first, the 6 subsequent cases the second direct effect, and the case in the health care worker would represent the third and indirect effect.

3_09 It is notable that the association of tuberculosis and AIDS was first described in the United States which on a global scale surely has a minor tuberculosis problem, with or without HIV infection. The reason why the US public could be alerted before that of any other country about the possible impact of HIV on the tuberculosis epidemiology is because the US disposes of an enviable quality surveillance system of notifiable diseases. There are two systems in place, actually. One is sensitive and rapid, and the second has an emphasis on specificity and is relatively slow. This slide deals with the sensitive and rapid system. All States report weekly

presumed cases of notifiable diseases to CDC which publishes them as aggregate numbers of cases in the weekly MMWR publication. The only thing of interest is the case count of presumed cases (some of which will be retracted in the specific system that follows a more refined and rigid case definition). What was done here was simply comparing the cumulative annual case number in a given week compared with the cumulative case number in the same week in the previous year expressed as a percentage change. At the beginning of the year the large amplitude from one to the next week is due to the small cumulative number at the beginning of the year. The graph shows how the curve becomes fairly smooth by about the middle of the year when it is already pretty well predictable what the remainder of the year has in store. Here, the provisional cases of 1984 in mid-year are predicted to decline by about 8% compared to 1983, and that's pretty much how it stays.

Here, the same comparison was made weekly for the year 1985 versus 1984. This red line shows a substantially different pattern by mid-year: the cases fail to decline and this observation holds until week 39, when this was published and the American public alerted to the problem. Quality surveillance is key to knowing what is going on.

3_10 This clip summarizes the complexity of several aspects that have been discussed up to here. Sex differences in the prevalence of infection with *M tuberculosis*, and risk differences for disease progression given infection have been discussed earlier. These 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 1. 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 considerably 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, relatively 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 Tuberculosis declined almost regularly in Switzerland since the 1940s (and likely longer, but with surveillance data too poor to document). In 1980, tuberculosis case rates in Switzerland were around 20 and in Tanzania around 50 per 100,000 population.

Subsequently, the emerging disparity is substantial: the exponential decline continues unchanged in Switzerland, while Tanzania simultaneously experiences an exponential increase. HIV has no impact on Switzerland, while its effect on tuberculosis in Tanzania is substantial and will leave a long-lasting imprint even now that the effect is seemingly halted by the increasing availability and use of HIV diagnosis and anti-retroviral treatment.

3_12 In most of western Europe, the course of the tuberculosis epidemic among the native-born population has shown a similar declining behavior as reported here from Denmark.

Also similar has been the observation of an increasing contribution by the foreign-born population to the total number of case. The increase is not solely due to an absolutely growing foreign population but also due the fact that the composition of the foreign-born has been changing gradually. Increasingly, persons immigrate from countries with a higher tuberculosis problem than those of traditional immigrants. The relative contribution to the total by tuberculosis among the foreign-born now exceeds 50% in many western European countries. It is nevertheless noticeable that the effect on tuberculosis among the in-country born population must be modest as its decline just continues. Tuberculosis is not that easily transmissible, transmission will largely occur indoors, and diagnosis with resulting curative treatment has substantially shortened transmissibility. Furthermore, even if tuberculosis is considered a large problem among some immigrant population segments, it is nevertheless relatively and absolutely still rare.

3_13 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. Usually we look cross-sectionally at age-specific morbidity in a given year. In 1930, the Norwegian Kristian Andvord demonstrated that a cross-sectional analysis alone fails to tell the whole story. Not only age matters, it also matters when one is born. We can thus also look at the epidemiology of tuberculosis within birth cohorts. Applying this to the data from Finland, we 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 of the 1922 birth cohort in this decade.

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 from that seen solely cross-sectionally. In each birth cohort morbidity peaked among the 20- to 24-year-old. What we 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 when their infection had been acquired more recently. Recency of infection 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. The seemingly discordant observation cross-sectionally versus birth cohort is thus a result of an improving epidemiologic situation: the high peak among the elderly seen cross-sectionally is not a sign of immunity senescence as one can sometimes read, it shows that the elderly were born when transmission was much worse than it is today and that their own birth cohort had experienced an enormous burden of tuberculosis, much in excess what the young experience today.

3_14 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?

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 or disrupting societal changes. 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.

4_02 Here are three survival curves for patients with sputum smear-positive tuberculosis in the pre-chemotherapy era. It shows that patients with transmissible tuberculosis may survive and remain infectious for a long time if left untreated, but ultimately 60%-80% succumb to it. Pulmonary tuberculosis, left untreated, is an ultimately highly fatal disease. Even if nowadays there might occasionally be a delay in diagnosis of several weeks, it is still early in a possibly up to 10 years lasting course, and even delayed treatment will still save many lifes and prevent a substantial proportion of transmissions in the community that could otherwise take place.

4_03 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 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.

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.

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. This approach to display adds a third component after we introduced age and cohort effects, this will reveal and period effect. Period effects are for instance famine or war, affecting at a given period of time irrespective or in addition to age and birth cohort.

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 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.

With this encouraging note we have reached the end of this presentation of the epidemiology of tuberculosis in western Europe over the past century, but there is one more slide containing information we should be aware of.

gdp While the data are now over ten years old, it is likely that the observations still hold: the tuberculosis epidemic shows a close correlation with the wealth of a population and is independent of population size. The smaller the gross domestic product, the larger the estimated tuberculosis incidence and vice versa: the wealthiest countries have currently the lowest tuberculosis burden. It's perhaps not always that straight forward, and there are some points one might raise here, but it is always and certainly food for thought.