Physica A 506 (2018) 476–485

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Excess tuberculosis-mortality in young women: High accuracy exploration

Sylvan Berrut [a], Peter Richmond [b], Bertrand M. Roehner [c,d,*]

[a] Swiss Federal Office of Statistics, Neuchâtel, Switzerland
[b] School of Physics, Trinity College Dublin, Ireland
[c] Institute for Theoretical and High Energy Physics (LPTHE), University Pierre and Marie Curie, Paris, France
[d] CNRS (Centre National de la Recherche Scientifique), France

HIGHLIGHTS

- The age-specific female/male death ratio informs us on immunity mechanisms.
- It reveals a notable peak between ages 5 and 25.
- This TB anomaly is used for probing the reliability of death statistics in developing countries.

ARTICLE INFO

Article history:
Received 6 February 2018
Received in revised form 3 April 2018
Available online 23 April 2018

Keywords:
Death rate
Testosterone
Male
Female
Tuberculosis

ABSTRACT

In a general way at all ages and for almost all diseases, male death rates are higher than female death rates.

Here we report a case in which the opposite holds, namely for tuberculosis (TB) mortality between the ages of 5 and 25, female death rates are about two times higher than male rates. What makes this observation of interest is that it occurs in all countries for which data are available (e.g. Britain, Switzerland and United States), and in all years from the end of the 19th century up to the time in the 1960s when TB became a very rare disease in all developed countries. The fact that this regularity holds despite a drastic reduction in the number of deaths is also noteworthy.

So far, the reason of this anomaly remains an open question but the effect is so accurate that it can be used for probing the reliability of mortality records. This will be explained in the case of developing countries. For instance, it turns out that in South African TB death data as published (and revised) by the "World Health Organization", female deaths were certainly under-estimated by a factor of two. Another implication of our results comes once they are combined with the finding of Bini et al. (2014). It is suggested that clearer insight may be gained by testing the levels of testosterone, progesterone and estrogens in TB patients (particularly in children and young adults) on the one hand and in control groups of healthy volunteers of same sex and age on the other hand.

* Corresponding author at: Institute for Theoretical and High Energy Physics (LPTHE), University Pierre and Marie Curie, Paris, France.
E-mail addresses: Sylvan.Berrut@bfs.admin.ch (S. Berrut), peter_richmond@ymail.com (P. Richmond), roehner@lpthe.jussieu.fr (B.M. Roehner).

https://doi.org/10.1016/j.physa.2018.04.065
0378-4371/

1. Introduction

According to a broad rule, at all ages and for almost all diseases (and particularly for infectious diseases) male death rates are higher than female death rates.[1] The paper is concerned with a case in which the opposite holds: for girls and young women, the death rate of tuberculosis is about two times higher than for males of same age. For the sake of brevity in what follows this will be called the *TB anomaly*. At first sight, it could appear as nothing more than a fairly insignificant anomaly. However, as explained in the following subsection, the history of science shows that finding the right explanation of anomalies has been a permanent source of progress.

1.1. Anomalies seen as an engine of scientific progress

In support of this claim, one can recall two famous "anomalies".

- The Fresnel (or Arago) spot experiment in one step proved that Newton's corpuscular theory of light was unsatisfactory.[2]

- The angular velocity of the rotation of the major axis of the orbit of Mercury is faster (by about 8%) than what Newtonian mechanics predicts. For planets this effect is called "perihelion precession" or "perihelion advance".[3]

It is worthwhile to observe that the previous anomalies are both very small effects. The Fresnel spot is a bright dot only about 0.1 mm in diameter. The ellipse of Mercury rotates with an angular velocity of 0.15 degree per century, of which the unexplained part is only 0.012 degree per century.

In short, the very identification of these anomalies and the test of their explanations relied on *accurate measurements*.

Compared with the previous anomalies the TB anomaly discussed in this paper is a fairly massive effect. This explains why, as described in the next subsection, it was identified nearly two centuries ago. However, it was never measured accurately.

1.2. Early identification of the TB anomaly

In 1831 a doctor from the "Hopital de la Charité", then one of the main hospitals in Paris, published a paper[4] in which he pointed out that there are more females than males among both TB patients and TB fatalities, particularly in young age groups. At that time the origin of TB was still unknown. Dr. Louis used the observation that the excess female mortality was special to TB and did not exist in other pulmonary diseases to infer that TB itself was due to a specific factor. Dr. Louis' observation was based on a fairly small sample of a few hundred patients but was confirmed in following decades by further observations. Moreover, his conjecture proved also remarkably farsighted for Robert Koch's discovery 51 years later of the bacterium that causes tuberculosis proved indeed that it was a very specific disease which had no connection with other common lung diseases.

As shown by this early paper, the question of excess TB mortality among women as well as its possible implications captured the attention of medical doctors very early and we will see that subsequently it was revisited many times. Yet, this excess rule was never stated with any accuracy as if, contrary to physics, medicine had nothing to gain from accurate measurements. That is why this question can serve to illustrate the methodological discrepancy between the approach of physics[5] on the one hand and of medicine (or biology) on the other hand. Thus, we believe that its significance extends beyond the specific problem investigated here.

1.3. Objectives of the present paper

In the previous subsection we reported observations made in Paris, but it is clearly unsatisfactory to limit the investigation to just one country. After all the observations could be due to local factors in which case it would be of little interest as a biological issue.

Thus, the first step is to examine other countries. If the same effect can be observed and is of similar magnitude, then there is a good likelihood that it is due to a real biological mechanism.

We have already said that we wish to present accurate measurements. In what sense will they be more accurate than in previous publications? Basically, we will focus on time periods and countries where the effect was the most apparent. This involves the following steps.

Selection of the time period. TB was a major cause of death until the discovery of antibiotics following World War II. In the 1950s and 1960s TB mortality fell drastically to the point that it has now almost disappeared in developed countries (see Table 1).

It is because after World War II TB mortality cannot be analyzed in a significant way that we will focus on data from the late 19th century and first half of the 20th century.

---

1 This rule seems to hold not only for humans but also more generally for primates [1], mammals and vertebrates [2].

2 This small spot appears at the center of a circular shadow.

3 A very similar effect (i.e. a movement produced by a central force) can be seen for the elliptical trajectory of a spherical pendulum, in which case the ellipse rotates with an angular velocity ω given by the Puiseux formula: $\omega \sim S/L^{2.5}$, where S is the area of the ellipse and L the length of the pendulum; as the proportionality constant involves only numbers and the acceleration of gravity g, it is unessential for comparative tests.

4 [3].

5 Above all the approach of physics means accurate well targeted measurements along with their comparative analysis.

Table 1
TB deaths by age-group in the United States, 1999–2014.
Source: CDC: Compressed mortality, Wonder database, 1999–2014.

	0–1	1–4	5–9	10–14	15–19	20–24	25–34	35-44
Female	10	16	8	5	11	43	93	156
Male	5	10	1	8	19	50	171	380
f/m	2.0	1.6	8.0	0.63	0.56	0.86	0.54	0.41

Notes: Although the trend agrees with expectation, clearly in the range $5-25$ in which one expects $f/m > 1$ the numbers of deaths are too small for their ratio to be really reliable. This means that the incidence of TB has become too small for the TB anomaly to be measurable.

Selection of the countries. TB remains an important disease in developing countries. Unfortunately, the health data published by developing countries often are not reliable. This is shown by the categorization introduced by the Statistics Division of the United Nations which collects such data. All developed countries are in category 1 which corresponds to reliable data whereas almost all developing countries, particularly in Africa, are in category 3 which corresponds to fairly uncertain data. If, as was done by previous authors, one uses data from the second half of the 20th century then one is compelled to use statistics from developing countries for the simple reason that elsewhere the disease had disappeared.

Moreover, in order to further increase the number of cases, previous authors (see the next section) used data covering broad time-spans of about 40 years. In contrast we use data over 3 or 5 years intervals which give more accurate time definition.

1.4. What can be achieved?

Apart from giving curves which define this anomaly accurately, what else can we achieve? As we are physicists, not biologists, it cannot be expected that we propose a biological model. However, we can do two things.

- We can show that the sociological explanation based on poor diet (see below) is incompatible with our data.
- We can define the basic requirements for a truly scientific explanation. The most important is that before trying to explain the anomaly one must put forward an explanation for the general rule. In other words, one must identify the general mechanism which accounts for the fact that females have lower mortality than males. Then, the anomaly will find a natural explanation in the fact that one of the factors involved in the general mechanism has an abnormal behavior for TB in young patients. We will see below that previous authors wish to explain the anomaly without having identified the general mechanism. As a result, such an explanation will necessarily appear as *ad hoc*.

2. Explanations proposed in previous publications

After a short description of the TB anomaly, we describe previous explanations suggested by historians and epidemiologists and we explain why the answers they proposed appear unsatisfactory.

In human populations females have a lower mortality rate than males at any age and for almost all causes of death [4]. It is therefore natural that the exceptions attracted the attention of epidemiologists. Here we concentrate our attention on tuberculosis. It is true that apart from tuberculosis there are a number of other infectious diseases (see below) which show a similar effect but almost all such diseases are childhood diseases (e.g. measles) which means most cases occur prior to the age of 5. For instance, in 1901 in the UK, 94% of the measles deaths occurred between the ages of 0 and 5. In the $(15, 44)$ age interval, the only one in which there is a substantial female excess mortality, there are only 42 deaths[6] (0.5% of the annual number). In other words, for all those diseases except tuberculosis the female excess mortality concerns a very small number of patients. However, for tuberculosis the mortality increases from the age 5 to age 25 which means that, especially in the developing world, hundreds of thousands of patients are concerned by the female excess mortality effect.

The explanations put forward fall in two categories, sociological and biological.

2.1. Sociological explanation: poor diet as a cause of vulnerability

Several papers published in the past three decades from 1990 to 2017 [5–7] propose an explanation based on an inappropriate diet. The thesis can be summarized as follows [6, p.9].

> "A widely held account is that a lack of bargaining power in the home associated with a shortage of paid work for women led to women having a much poorer diet than men, which lowered their resistance to infections. In 1990 Michael Anderson argued that this was the underlying reason for the relatively high female mortality compared to that of males observed [in 19th century Britain] in poor agricultural areas and regions dominated by heavy industry."

A similar thesis was presented independently for the Netherlands by Angélique Janssens:

6 Website of the UK Office of National Statistics, vital rates.

> "We have been able to ascertain that a considerable part of maternal mortality in the period 1875–1900 can be attributed to respiratory TB for which adequate nutritional intakes are highly relevant".

What should one think of this explanation?
A piece of evidence that would provide a solid basis for this explanation would be statistics for the respective food intakes of boys and girls. Needless to say, no data of that kind are available at country level. Thus, one must rely on the belief that it made sense for families to favor their sons at the expense of their daughters.

The main problem with this explanation is that the excess-female mortality is not limited to the 19th century. In fact, as will be shown below in Fig. 1, it extends well into the 20th century including areas such as California or New York State which are not "poor agricultural areas". By extending their analysis to the 20th century, the aforementioned authors would have been able to identify this difficulty.

In short, we do not say that diet played no role whatsoever, but it is certainly not the main explanation for this effect.

2.2. A biological explanation based on the role of sex hormones

In a sense the excess-female mortality effect could be called the "Garenne effect" after the name of the epidemiologist Michel Garenne who from 1991 to 1998 [4,8,9] devoted much time to the study of this effect.

The study started from an observation made in rural Senegal in 1990 showing female excess mortality after measles vaccination. It was not until 8 years later that an explanation was proposed.

Positing a link between the hormonal and immunological systems seems of course a natural explanation for an effect which affects male and females differently.

An ad hoc explanation.

In Garenne et al. [4] the authors say that "there is growing evidence that sex hormones regulate the Th1/Th2 balance". Th1 and Th2 (Th refers to the thymus where these white cells are produced) are two sorts of white cells which eliminate foreign bodies, e.g. cells infected by a virus or cancer cells. It turns out that the female hormone progesterone promotes the production of Th2 cells whereas the male hormone testosterone favors the Th1 cells. To close the argument one only needs to observe that the Th2 cells seem to develop weaker resistance to bacteria than Th1 cells.

Obviously, this model was designed for the specific purpose of explaining excess-female mortality in an age interval during which the concentration of progesterone in the blood is fairly high. Unfortunately, the model does not say what makes this mechanism specific to TB. In order to be really convincing the model should explain *other effects* than the one for which it was designed.

The fact that the authors do not give any corroborating evidence once again denotes a lack of comparative perspective. In physics, when a new effect has been identified, the first task is to determine its multiple implications. For instance, surface tension explains why some insects (e.g. water striders) can walk on water, but it explains also many other observations, for instance the "tears of wine" phenomenon (a detailed description can be found on the Internet).

In search of corroborating evidence.

Starting from the fact that high levels of progesterone inhibit the fight against TB-like bacteria, what additional observational tests can one propose?

First, we must find situations in which the progesterone level is particularly high. Such situations should be marked by an excess-female vulnerability to TB. In men or postmenopausal women the concentration of progesterone in the serum of the blood is of the order of 1 nanogram per milliliter of blood serum. For young non-pregnant females it is of the order of 5 ng/ml (low at the beginning of the 28-day cycle and higher at the end). Finally, during pregnancy it is on average of the order of 50 ng/ml. In short, the concentration is really much higher than in men only during pregnancy.

Thus, a testable prediction of the progesterone model would be a high incidence of TB in women who have several children in succession as compared with women who have only one child or none at all. Naturally all other conditions should be similar and in addition the test should be made in a time period before the BCG vaccination became commonly used.

The authors of [4] mention a fact which, at first sight, seems to go in the right direction. They say that diseases such as rubella, influenza and tuberculosis "are more severe during pregnancy when the level of progesterone dramatically increases" but they give no evidence apart from the well known case of rubella, which however is of a different nature in the sense that it is the embryo which suffers rather than the mother.

2.3. Toward a clearer understanding of the general rule

In the introduction we emphasized that before one can propose a satisfactory explanation for the anomaly one must have an understanding of the general rule. Some recent papers, e.g. Neyrolles and Quintana [10] and Bini et al. [11] go in this direction.

A look at the recent biological literature suggests that there is not yet any real consensus about why males have a higher mortality in most diseases except tuberculosis. An interesting paper by Bini et al. [11] offers experimental evidence based on the reactions observed in mice. The paper starts with the observation that TB is twice as common in men than in women.

However, the authors are well aware of the TB anomaly. It is true that for an experiment on mice the analog of the human 5-25 age-interval would correspond to a very narrow age-group.
The paper's abstract closes with the following sentence: "male mice are more susceptible to tuberculosis than females and this was prevented by castration suggesting that testosterone could be a tuberculosis susceptibility factor". This suggests an explanation for the general rule.

If correct, this result needs of course to be corroborated through tests on other infectious diseases and also on other animals. Is this rule valid only for mammals or does it also hold for other model animals, e.g. Zebra fish or Drosophila?
We raise these questions but hold out little hope that further experiments will be done in this direction for, unfortunately, in biology there is no tradition nor inclination for comparative investigations.

2.4. Death rate, incidence rate, fatality rate

In a general way the death rate μ can be decomposed in the following way:

$$\mu = \frac{\text{deaths}}{\text{population}}, \quad F = \frac{\text{deaths}}{\text{affected population}}, \quad I = \frac{\text{affected population}}{\text{population}}$$

$$\text{Death rate } (\mu) = \text{Fatality rate } (F) \times \text{Incidence rate } (I)$$

The fatality rate which describes the severity of the disease is likely to be of biological nature, whereas the incidence rate which describes how fast the disease spreads is a mixed factor which reflects both biological features, e.g. the mode of transmission and sociological conditions, e.g. the frequency of social interactions.
More precise conclusions will become possible once incidence and fatality rate data become available.

3. TB female/male death ratio: accurate evidence

3.1. Measurements

In previous studies the data from many countries and many years (typically 1950–1989) were lumped together. Thus, in [8] the smallest areas considered were whole continents: Europe, North America (which mixes the US and Mexico), Latin America and so on. In [4] the graphs were drawn for the whole world. Such a procedure of data aggregation precluded any serious comparative analysis.

In the present paper we consider single countries (or even subareas of countries) over time intervals that were specifically calibrated to be the smallest intervals able to keep the statistical fluctuations at an acceptable level.

Fig. 1a,b,c,d show the TB anomaly between 1880 and 1960 and between the ages of 10 and 25. In the decades after 1970 the number of deaths due to TB became very small (except in old age). For instance, in the US in the time interval 1999–2015 and for all the age groups from birth to 45 years the annual number of deaths due to respiratory TB averaged only about 40. For that reason the effect becomes impossible to test after 1960.

The fact that this effect is seen not only in the US but also in Switzerland and Britain indicates that it is probably not due to a statistical artifact.

Fig. 2 shows the f/m death ratio for all causes of death for several European countries in 1906.[7] It can be seen that the age interval in which $f/m > 1$ is basically determined by the TB death ratio. A natural question is how this squares with the fact that for almost all diseases except tuberculosis f/m was smaller than one.
This is due to the fact that TB was by far the dominant disease. Here are some data for the number of deaths in France in 1906:

TB: 87, 091 Cancer: 27, 306 Heart diseases: 49, 889

If to tuberculosis one adds pneumonia which was often how tuberculosis ended one gets a total of 122,884 deaths. Thus, other diseases will reduce the amplitude of the f/m peak but they cannot lower it under 1.

4. Discussion of the TB anomaly

4.1. Female excess or male curtailment?

Is this effect due to an excess of female deaths or to an "abnormally" low number of male deaths? In an attempt to answer this question separate male and female data are shown in Fig. 1a,b. (male in black, female in red). What should one understand by "normal" curves? The term "normal" is understood here as "most common". The common pattern is that in a log–log plot the infant death rate is a downward straight line until the age of 10 after which it starts fairly suddenly to go upward [13]. The inset graphs in Fig. 1a,b show that the female curves begin to level off already around the age of 4. As a result they come above the curves of the male death rates and remain higher until the age of 25. Thus, it is the female rate (not the male rate) which behaves in an unusual way. In other words, the phenomenon is indeed an excess-female mortality.

[7] In addition it can be noted that for Japan the curve is very similar.

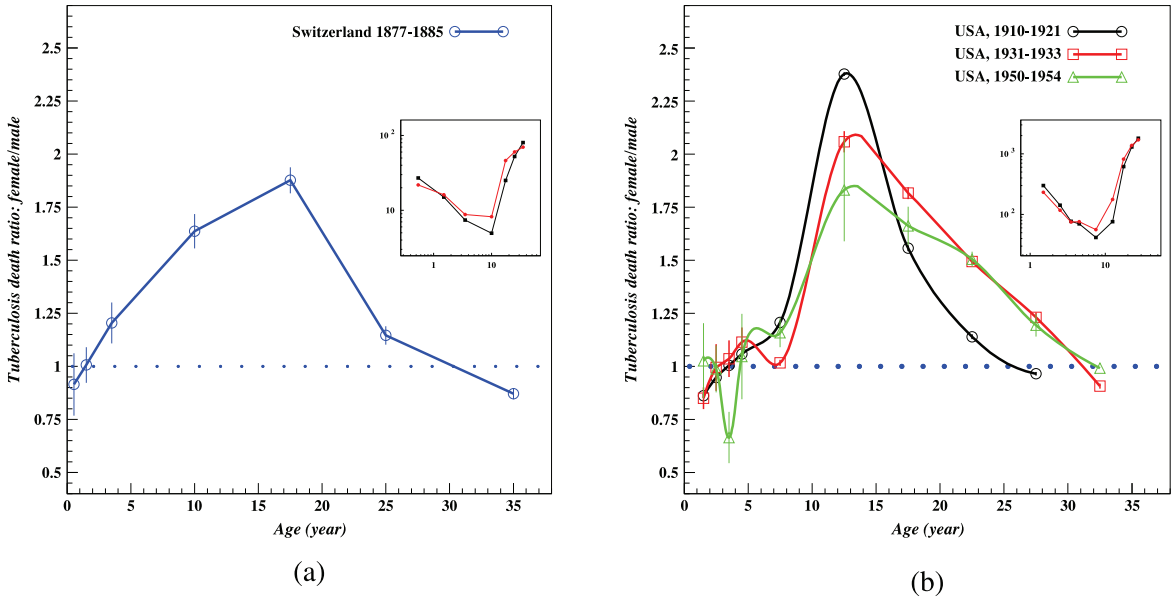

Fig. 1a, b. TB death ratio female/male by age in Switzerland and the US. More precisely TB refers to TB of the lungs. In the Swiss statistics it is the word "phthisis" which is used instead of TB. The error bars are defined as $\pm\sigma$ where σ is the standard deviation of the average. It should be noted that for the inset of Fig. 1b the colors do not have the meaning given in the legend of the main figure. In fact, the two insets show separately the female (upper line in red) and male (lower line in black) TB death rates. The purpose is to show that it is the male curve which looks "normal" whereas the female curve stops falling too early; note that the inset of Fig. 1b is for 1910–1921. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Source: Switzerland: Mouvement de la population de la Suisse 1877–1885, the data are available on the website of the "Office Fédéral de la Statistique", in the years after 1885 the death data by cause, age and sex were no longer included. USA: Bureau of the Census, Mortality Statistics, various years.

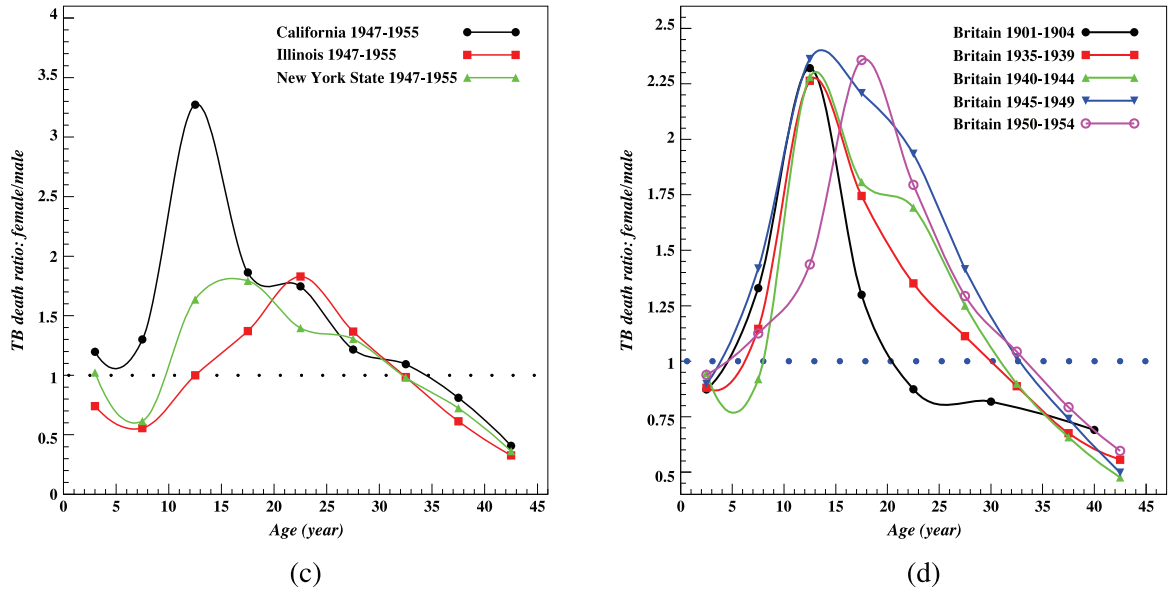

Fig. 1c, d. TB death ratio female/male by age in 3 US states (white population only) and in Britain. The error bars are rather small and have been omitted for the sake of clarity; on average the coefficient of variation is of the order of 4%.
Source: Vital Statistics of the United States; website of the British "Office of National Statistics", many thanks to Ms. Justine Pooley for her help.

4.2. Exogenous or endogenous?

As always in such situations, once the possible incidence of a recording artifact has been excluded, the effect can be due to exogenous or endogenous factors. Here exogenous would mean more contacts with pathogens or other external factors whereas endogenous would refer to physiological factors.

A possible exogenous factor which comes to mind is an occupational hazard. Let us examine this possibility more closely. The age interval over which the effect is observed is fairly broad. However, it is the starting age which really matters. Why? Because, once TB cases in excess have appeared the disease will develop through its own dynamic in the sense that it will

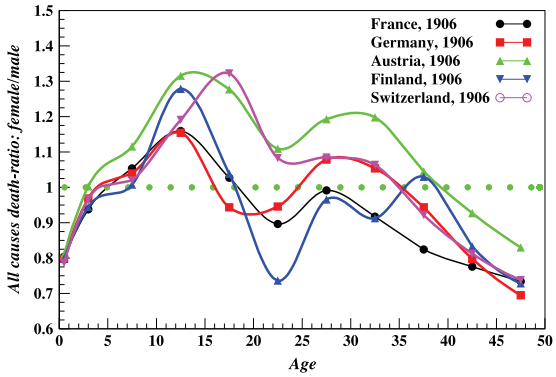

Fig. 2. All causes death ratio, female/male. The fact that the curves follow roughly the TB death ratio yet with a markedly smaller amplitude shows two things (i) the dominant role of TB (see text for detailed figures) (ii) substantially lower f/m ratios(actually lower than 1) for other diseases.
Source: Bunle [12].

progress in each affected individual and also spread by contagion to other persons. If this argument is accepted, how should one determine the starting age? In the graph the data points are shown with error bars which correspond to $\pm\sigma$. In order to raise the confidence level from 0.68 (which corresponds to $\pm\sigma$ to 0.96 (which corresponds to $\pm 2\sigma$ we will consider that the starting point occurs when the ratio becomes equal to $1 + 2\sigma$. This leads to a starting age of 5 in Switzerland and 6 in the US. The important point is that these ages are well before any industrial occupational activity. The only kind of activity that one can think of at that age would be domestic, for instance farm work. In most countries, the age of 6 marks the beginning of school attendance although it is far from clear why this should lead to an f/m anomaly.

4.3. Are there other diseases with more female than male deaths?

Recall that in the first half of the 20th century tuberculosis was the dominant cause of death. This makes the previous anomaly quite noteworthy. However one needs also to examine whether there are other diseases for which female deaths outnumber male deaths. More precisely, we wish to see if there are other diseases which show a female/male death ratio over 1 in the age interval 5-25?
A systematic investigation of British data for all the diseases mentioned in the International Classification of 1901 leads to the following findings.

- Code 60, measles.

$(0, 5) f/m = 0.88,\ (5, 15) f/m = 1.14,\ (15, 44) f/m = 2.00$. However, as already said, the 15, 44) age interval corresponds to a very small number of cases.

- Code 740, anemia and leucocythemia (nowadays rather called leukocytosis, i.e. white cells in excess).

$f/m \sim 3$ in the age interval 10–45. However, there are only few deaths. In successive 5-year age groups the numbers of deaths for this code number are under 100.

- Code 1060, cerebral hemorrhage and embolism.

$f/m \sim 2$ in the age interval 1–25. There are less than 30 deaths in each 5-year age group.

- Code 1810, burns and scalds.

This was the most puzzling finding. In the age interval 5–20, $f/m \sim 3$; then in 20–45, $f/m \sim 1$; finally from 45 to 85, f/m is again about 3. As females spend more time in the kitchen than do males, it is of course understandable that they are at higher risk but it is less clear why this effect is *not* seen in middle-aged females.

In short, apart from the case of burns, for the age intervals under consideration, the other cases are of minor importance in terms of death numbers.

5. Tuberculosis death ratio in developing countries

In developed countries TB mortality has become close to zero except in old age.[8] However, in many developing countries TB is still an important disease. Can the f/m effect be observed in such countries?

[8] In what follows age groups of older adults will be left aside. There are two reasons for that. The first is of course because the f/m effect occurs in early years. In addition, one should remember that because of atypical clinical symptoms the diagnosis of tuberculosis in elderly people is rather uncertain [14].

Table 2a
TB death ratios f/m and m/f in the age groups (0,15) and (15,60) in the US. *Source:* Vital Statistics of the United States, Wonder database of the "Centers for Diseases Control" (CDC).

Year	Female/male $I_1 = (0, 15)$	Male/female $I_2 = (15, 60)$
1910	1.2	1.33
1931	1.1	1.27
1943	1.2	1.71
1950	1.2	2.16
1954	1.1	2.41
1999–2015	–	2.64

Notes: The symbol – means that the ratio is not well defined because the numbers of deaths are too small. It can be seen that for I_1 the ratio female/male remains stable around a value of 1.1. In contrast after 1931, as the deaths in the sub-interval (35,60) of I_2 become predominant, the ratio male/female increases from 1.3 to 2.6. Compared with Fig. 1b, the values in the column I_1 may appear too small; this is due to the fact that the f/m ratio for I_1 is not the average of the ratios in the years from 0 to 15 but rather a weighted average; a more detailed explanation can be found in the text.

5.1. Defects of the WHO data base

Before we can answer this question we must examine what statistical data are available. The data of the "World Health Organization" (WHO) provide a broad coverage for almost all countries and TB features at the top of the list of diseases. However for the objective that we have in mind there are three difficulties.

• The data by age are limited to only three age groups, namely: $I_1 = 0 - 15,\ I_2 = 15 - 60,\ I_3 = 60^+$.

• In many developing countries the quality and completeness of the data is not good. The WHO distinguishes 3 categories which are represented by 3 colors: "magenta" means very incomplete, "cyan" means fairly complete, "blue" means good quality data. Developed countries are blue, semi-developed countries are cyan and almost all African countries are magenta. For our purpose this is quite unfortunate because it means that for the countries where TB may be most prevalent there are in fact no reliable data. That is why we will focus on semi-developed countries.

• There is another cause of uncertainty due to the way the data are reported. In the table the numbers of deaths are expressed in thousands but as there is only one decimal digit a number such as 0.1 could mean 0.051 or 0.149 which means that there is an uncertainty of $(0.149 - 0.051)/0.1 = 100\%$. In other words, the smaller the number of deaths, the lower its accuracy.[9] For the same reason all data for developed countries are reported as being 0.0; this only means that the real death numbers are less than 0.05 thousand $= 50$. Yet, in countries with a small population this may still represent a sizable death rate.

5.2. Test of the f/m effect in developing countries

Because of the limitation in the number of age-groups we cannot test the f/m effect directly. The age group I_1 is a mixed age-group in the sense that, as shown in Fig. 1b,c,d, in the interval $(0, 5)$ (or sometimes $(0, 7)$) the ratio f/m is smaller than 1. The age-group I_2 is even less satisfactory because the ratio f/m is smaller than 1 in the interval $(25, 60)$.
How should one perform the comparison?

For both I_1 and I_2 he WHO data allow us to compute the ratio f/m. They are given in Table 2b for several countries.

Then, we must compare these ratios with the same ratios for a country (for instance the US) for which there are detailed results for the years $(0, 15)$. This is done in Table 2a.
Compared with the curves in Fig. 1b the ratios given for I_1 may appear too small. This impression is due to two circumstances.

(1) The f/m value for I_1 is *not* the average of the annual ratios but rather the number of female deaths divided by the number of male deaths in the whole interval.
Not surprisingly, there are more deaths in the interval $(0, 5)$ than in the interval $(5, 15)$. For 1931 the data are as follows.

$$(0, 5):\ m = 1,060,\ f = 867,\ f/m = 0.82 \quad (5, 15):\ m = 571,\ f = 674,\ f/m = 1.18$$

In fact, f/m climbs strongly only after the age of 15; thus, for $(15, 20)$ one gets: $f/m = 1.78$.

(2) A second reason is the fact that Fig. 1b does not give the f/m values for all separate years in the interval $(0, 10)$; as a result, the curves over-estimate f/m in this interval.

Fig. 3 shows that the parts of the curves in the age-interval $(0, 15)$ keep the same structure. On the contrary, in the age-interval $(15, 60)$ the old age component becomes more and more predominant especially in the decades after 1940. If one

[9] Obviously this is not a sound way of reporting because it adds a "reporting uncertainty" to the "recording uncertainty". The data should be reported with the same number of digits whether the figures are small or large, e.g. 0.36 and 36 instead of 0.4 and 36.1.

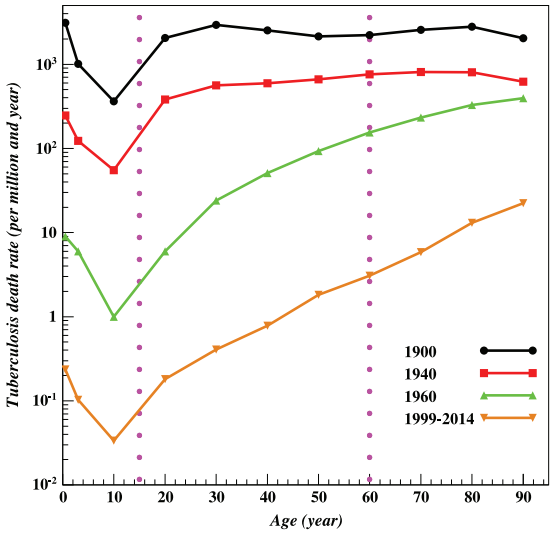

Fig. 3. TB death rate in the United States. From 1940 to the end of the 20th century the old-age component becomes more and more predominant. *Source:* Linder and Grove [15, p. 248–254]; Grove and Hetzel [16, p. 378–469]; Wonder database of the Center for Diseases control" (CDC).

Table 2b
TB death ratios f/m and m/f in the age groups (0,15), (15,60) in various countries.
Source: World Health Organization 2011: Mortality and burden of disease estimates for WHO member states in 2008.

Country	Female/male $I_1 = (0, 15)$	Male/female $I_2 = (15, 60)$
China	1.0	1.60
India	1.2	1.50
Philippines	0.91	1.64
South Africa	0.84	3.51
Thailand	1.0	1.67

Notes: The data are for 2008. The value 3.51 for I_2 in South Africa is an outlier not only with respect to the other countries but also with respect to the whole range 1.3-2.6 displayed in Table 2a. Therefore, it is likely that this figure is not correct; probably female deaths were under-estimated by a factor of 2.

remembers that, as shown in Fig. 1d (and the continuation of the curves beyond the age of 42) $f/m > 1$ in the age-interval (15, 30) but $f/m < 1$ in the age-interval (35, 60), it becomes clear that over the interval (15, 60) the ratio m/f will become larger as old-age deaths become predominant. This is indeed what appears in Table 2a.

With the exception of South Africa, the figures by country given in Table 2b are consistent with the longitudinal data for the United States given in Table 2a. The case of South Africa shows that, most likely, female deaths were under-reported by a factor of 2.

In other words the f/m effect reported in this paper can be used to probe the reliability of the data published by national statistical agencies. As a matter of fact, according to the accompanying explanations, the data published in the WTO report are not exactly identical to the figures provided by member states but have been revised by the WHO to ensure "cross national comparability". This makes the discrepancy observed in Table 2b even more surprising.

6. Conclusion

The female/male death rate ratio for TB in all industrialized countries for which appropriate data are available during the late 19th century through to the mid-20th century is greater than unity for the age range 10–25 (in some cases this age interval may extend to 35). Whereas evidence given in previous publications relied on a pool of aggregated data comprising numerous countries and time spans extending over several decades, here we presented evidence based on single countries (Switzerland, United States, United Kingdom) and even single US states (California, Illinois, New York) over short time intervals of 3 or 5 years. These data revealed that the TB anomaly is characterized by a great stability: in age the anomaly extends from 10 to 25 (between 5 and 10 f/m is higher than 1 but close to 1) and in amplitude it is almost always comprised between 2 and 2.5.

The fact that the TB anomaly can be observed in prosperous areas such as California (1947–1955) clearly disqualifies the "poor diet" explanation.

Secondly, thanks to the stability of the TB anomaly, we can infer that in some developing countries (we pointed out the case of South Africa) deaths from TB are being under-reported by factors as large as two. In this connection it has been

suggested that such under-reporting may be the result of stigma faced by women with TB. A study in India found that male patients with TB expected their wives to care for them but infected wives rarely received care. Thus, married women may try to hide their symptoms instead of seeking help [17].

The rule suggested in Bini et al. [11] is that testosterone (the main male hormone) and progesterone (a female hormone involved in pregnancy) impair the immune system whereas estrogens (another family of female hormones) activate it. If this rule could be firmly established through a broad series of experiments that would constitute what we called the general rule (namely that females have a more active immune system than males). However, this rule does not explain the TB anomaly. Some 187 years after Dr. Louis's observation this remains an open question.

Acknowledgment

We wish to express our sincere thanks to Ms. Justine Pooley of the UK "Office of National Statistics" for introducing us to detailed British mortality data.

References

[1] A.M. Bronikowski, J. Altmann, D.K. Brockman, M. Cords, L.M. Fedigan, A. Pusey, T. Stoinski, W.F. Morris, K.B. Strier, S.C. Alberts, Aging in the natural world: Comparative data reveal similar mortality patterns across primates, Science 331 (6022) (2011) 1325–1328.
[2] T.H. Clutton-Brock, K. Isvaran, Sex differences in ageing in natural populations of vertebrates, Proc. R. Soc. Lond. [Biol] 274 (1629) (2007) 3097–3104.
[3] Dr. Louis, Sur la fréquence relative de la phthisie chez les deux sexes (Respective frequency of tuberculosis by gender), Annales d'Hygiène publique et de Médecine Légal 1 (6) (1831) 46–51.
[4] M. Garenne, M. Lafon, Sexist diseases, Perspect. Biol. Med. 41 (2) (1998) 176–189.
[5] M. Anderson, The social implications of demographic change, in: FML Thompson (Ed.), The Cambridge Social History of Britain, 1750–1950, in: People and Their Environment, vol. 2, Cambridge University Press, Cambridge, 1990.
[6] A. Hinde, Sex differentials in mortality in nineteenth-century England and Wales, in: Paper presented at the Economic History Society Conference. Cambridge, 1-3 April 2011.
[7] A. Janssens, A natural female disadvantage? Maternal mortality and the role of nutrition related causes of death in the Netherlands, 1875–1899, in: 28th IUSSP, International Union for the Scientific Study of Population, Cape Town, 29 October–3 November 2017, 2017.
[8] M. Garenne, Sex differences in measles mortality: A world review, Int. J. Epidemiol. 23 (3) (1994) 632–642.
[9] M. Garenne, O. Leroy, J.P. Beau, H.Sene.I. Whittle, A.R. Sow, Efficacy, safety and immunogenecity of two high titer measles vaccines. A study in Niakhar, Senegal, Final Report, ORSTOM (Office de la Recherche Scientifique et Technique Outre-Mer), Population et Santé, Dakar, Sénégal, 1991. [The ORSTOM has become the IRD (Institut de Recherche pour le Développement) in 1998].
[10] O. Neyrolles, M.L. Quintana, Sexual inequality in tuberculosis, PLoS Med. 6 (2009) e1000199.
[11] E.I. Bini, D.M. Espinosa, B.M. Castillo, J.B. Payán, D. Colucci, A.F. Cruz, Z.L. Zatarain, E. Alfonseca, M.R. Pardo, O. Bottasso, R.H. Pando, The influence of sex steroid hormones in the immunopathology of experimental pulmonary tuberculosis, PLoS One 9 (4) (2014) e93831.
[12] H. Bunle, Le mouvement naturel de la population dans le monde de 1906 à 1936 (Vital rates from 1906 to 1936 in many countries in the world), Les Éditions de l'Institut d'Études Démographiques, Paris, 1954.
[13] S. Berrut, V. Pouillard, P. Richmond, B.M. Roehner, Deciphering infant mortality, Physica A 463 (2016) 400–426.
[14] T.Y. Thomas, S. Rajagopalan, Tuberculosis and aging: A global health problem, Clin. Infect. Dis. 33 (7) (2001) 1034–1039.
[15] F.E. Linder, R.D. Grove, Vital Statistics Rates in the United States 1900-1940, US Government Printing Office, Washington DC, 1947.
[16] R.D. Grove, A.M. Hetzel, Vital Statistics Rates in the United States 1940–1960, US Government Printing Office, Washington DC, 1968.
[17] M. Connolly, P. Nunn, Women and tuberculosis, World Health Stat. Q. 49 (2) (1996) 115–119.