Postnatal death rate spikes due to viral and bacterial diseases

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SUMMARY

Background: After birth, setting up an effective immune system is a major challenge for all living organisms. In a previous paper (Berrut et al. 2016) it was shown that this process can be explored by using the age-specific post natal death rate (AS-PNDR) as a kind of sensor. This is made possible because between birth and the age of 10 the death rate decreases with age as a smooth hyperbolic function.

Aim: To report how one can decipher the ups and downs of the AS-PNDR of specific diseases and to see if the predictions made in Berrut et al. (2016) are confirmed.

Method: The AS-PNDRs of viral and bacterial diseases were compared in a time period, namely 1910-1921, where these rates were greatly amplified compared to what they are nowadays. Data from Switzerland and the United States were used.

Findings: The AS-PNDRs of measles, tuberculosis and influenza were found to display spikes and bulges in the age intervals where they were expected, i.e. around 10 days for the spike of viral infection and around 300 days for the bulge due to bacterial infection. In addition the AS-PNDR of measles shows a peak around 500 days which was not expected and remains so far unexplained.

Conclusion: During the first years after birth the development of the immune system goes through several steps progressively shifting from the immunity transmitted by the mother to autonomous immunity. The response to pathogens can be used as a probe which permits to explore this process in a macro-biological perspective.

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Introduction

The study of age-specific postnatal death rate (AS-PNDR) has attracted less attention than the study of aging (e.g. Sas et al. 2012 for a broad conceptual interpretation). The exploration of statistical evidence for a range of species including humans showed the following features (Berrut et al. 2016).

(1) The AS-PNDR decreases between birth and a critical age t_c after which it increases in the way described by Gompertz's law (Gompertz 1825). For humans t_c is equal to about 12 years. For that reason, in what follows, the term infant mortality will be used in an extended way to cover the whole interval $(0, t_c)$ instead of only the first year.

(2) In contrast with Gompertz's law which is an (increasing) exponential function (with a doubling time of about 10 years), the AS-PNDR is a (decreasing) hyperbolic power law function: $\mu_b \sim 1/t^\gamma$ where μ_b denotes the infant death rate and t the age. The exponent γ is comprised between 0.6 and 1.

(3) Superposed to the hyperbolic fall, there may be spikes due to temporary mortality surges. Our purpose in this paper is to show that such ups and downs are not just random fluctuations but in fact *do have* a definite interpretation in the sense that they express the kind of exogenous factors to which the organism is confronted.

In a previous investigation (Berrut et al. 2016) it was shown that for fish the "all causes" AS-PNDR displays a spike which corresponds to the moment t_1 when the yolk sac is depleted. During the time interval between hatching and t_1 the fish can still breath through their skin and get nourishment from their yolk sac. In other words, for fish it is t_1 which is their real birth time. That is why on their "all causes" AS-PNDR there is a clearly visible spike around t_1. More details can be found in Kovacks-Nolan et al. (2012) and Berrut et al. (2016).

For humans the temporary spikes are almost invisible on the "all causes" AS-PNDR (Fig. 1a). However, on the AS-PNDR of *specific diseases* two protrusions are clearly identifiable: one occurs 10 days after birth (Fig. 1b) and the second around the age of 300 days (Fig. 1c). In what follows it will be shown that the first is related to viral infection whereas the second is related to bacterial infection.

By going back in time several decades ago when infant mortality was much higher than it is currently, it is possible to get a magnified view of these peaks.

Method and data

Method

Four diseases were selected: (i) measles and influenza which are due to viral in-

fection (ii) tuberculosis of the lungs and scarlet fever which are due to bacterial infection. Measles, scarlet fever and tuberculosis are easily identifiable and should therefore lead to few misdiagnoses. On the contrary, it seems that in the past there was no clear distinction between influenza and pneumonia deaths[1]. For our investigation this kind of confusion matters because, in contrast to influenza, pneumonia can be either viral or bacterial.

Nowadays the number of deaths due to such infectious diseases is very low. For instance, according to the "Wonder" database of the "Centers for Disease Control" (CDC) in the US from 1999 to 2015 there were only 12 deaths due to measles, i.e, less than one per year. Therefore, in order to carry out our investigation we must go back to earlier times in which such deaths were more frequent. Such early years will provide so to say a magnification of the phenomenon that we wish to study. In the next subsection it is explained why we selected the period 1910-1921.

The aim of our study is to measure the response function of the population to pathogen outbreaks. However, for our procedure to make sense one must assume that all individuals are more or less confronted to the same contagion shocks. This assumption is fairly acceptable for the age range in which the spikes occur, namely before the age of three (about 1,000 days). The assumption would be less justified for school-age children who are in contact with a broader range of pathogens than children at home. The papers by Wilkinson et al. (2006) and by Tsagris et al. (2012) give good illustrations of the importance of the prevalence factor.

Data

The present investigation focuses on the period 1910-1921 in the United States for three reasons.

(1) Apart from the United States, there are few countries (among them is Switzerland) which have made all their vital statistics freely available on the Internet.

(2) The US Bureau of the Census started to publish detailed infant death statistics in 1910. Until 1921 they were published in the "Mortality Statistics" volumes but from 1922 on they were included in the "Birth, Stillbirth and Infant Mortality Statistics" volumes which currently are not available on the website of the CDC.

(3) Were the numbers of deaths sufficient to make the results statistically reliable? In order to get an idea of their order of magnitude one can examine the numbers of deaths in the first year after birth; in 1910 they were as follows:

Measles: $1,500$ Scarlet fever: 300 Influenza: 520 Tuberculosis of the lungs: 900

As shown in Fig. 1 for three of these diseases the statistical fluctuations were quite

[1] In the US "Mortality Statistics" volume for 1918 it is observed that "doubtless many cases were returned as influenza when the deaths were caused by pneumonia, and vice versa".

moderate. However for “scarlet fever” they are fairly large especially in the age range between one and 100 days. For that reason this case was omitted in what follows.

The time intervals $(1910-1917)$ and $(1918-1921)$ were treated separately in order to see the effect of the influenza surges that occurred in 1918 (by far the largest), 1919 and 1920

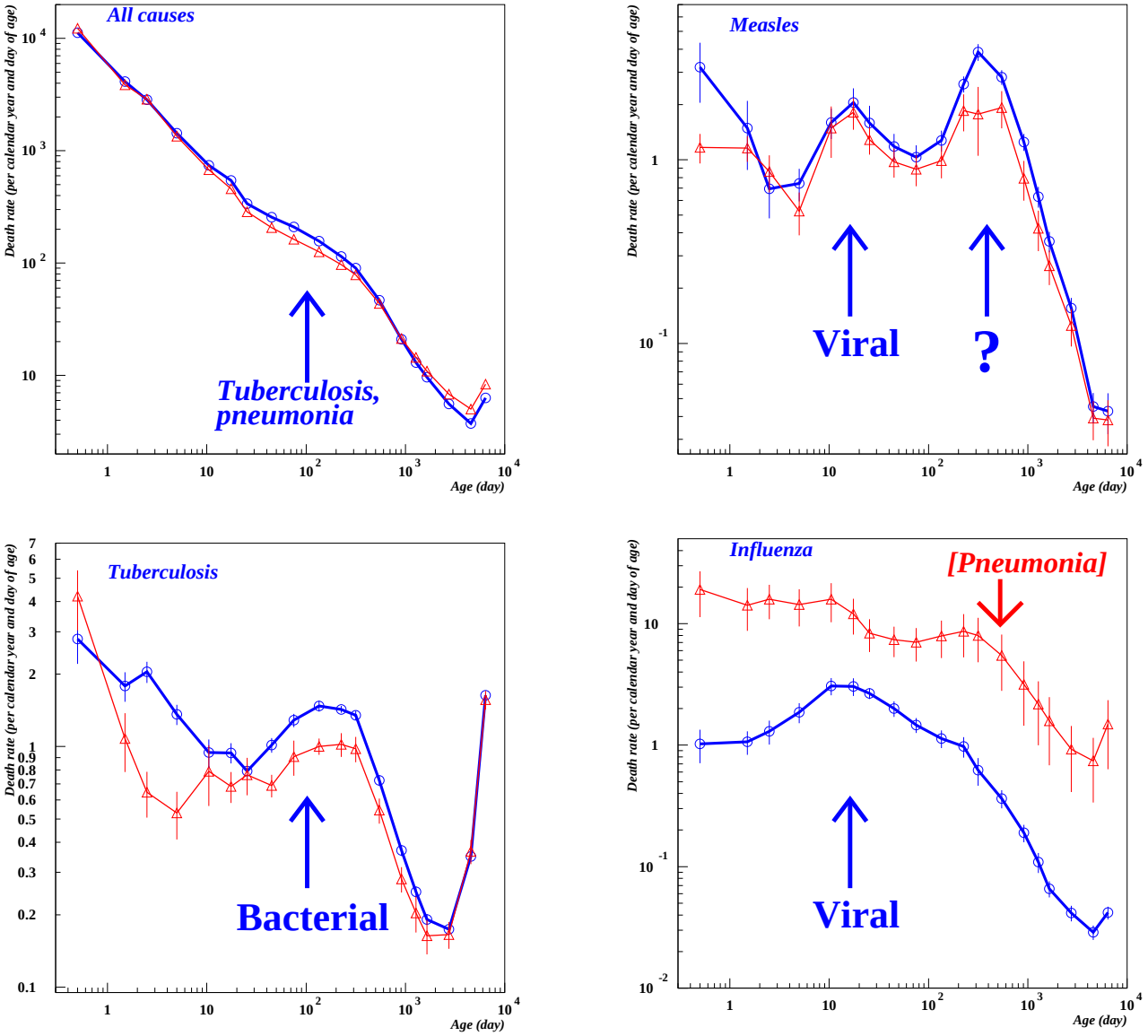

Fig. 1a,b,c,d Age-specific infant death rates in the United States, 1910–1921. The word “infant” is used here in its extended meaning as the age-interval during which the mortality rate decreases, i.e. it extends from 0 to 12 years (or 4,400 days) of age. The circles and triangles correspond to the years 1910–1917 and 1918–1921 respectively. Two precisions are in order: (i) Panel (c) refers more specifically to “tuberculosis of the lungs”. (ii) All data are for the so-called “death registration area” of the United States. In 1910 it comprised 58% of the population and in 1921 it comprised 82%. The error bars are $\pm\sigma$ where σ denotes the standard deviation of the average over successive years. *Sources: Bureau of the Census: Mortality Statistics, years 1910–1921.*

Results

Viral and bacterial death spikes

The results of our investigation are summarized in Fig. 1a,b,c,d. All graphs are log-log plots which means that straight lines correspond to power law functions. The curves with the circles are for $(1910-1917)$ whereas those with triangles are for $(1918-1921)$. Not surprisingly, they are very similar except in the case of influenza. For the sake of clarity the error bars were drawn as $\pm\sigma$ where σ denotes the standard deviation of the average of successive years[2].

Fig. 1a shows that the "all causes" AS-PNDR is very much a straight line with a hump in the range $(80-1,000)$. The exponent is: $\gamma = -0.83 \pm 0.05$ (the coefficient of linear correlation is 0.992 and ± 0.05 is the confidence interval for a probability level of 0.95).

The two cases which are the most reliable are "measles" and "tuberculosis" because, as already mentioned, they are devoid of misdiagnoses. The curves for measles display a peak of amplitude 3 around day 10, the amplitude being defined as the ratio of peak rate to initial rate. The curves for tuberculosis display a peak around day 300 which has an amplitude of about 2.

The viral peak appears also on the influenza curves. In this case one is not surprised to see also a bacterial bulge because of the confusion already mentioned with pneumonia.

Whereas the previous peaks were predicted, in addition there is a second peak on the measles curves which came as a surprise. This peak can hardly be explained away by misdiagnoses because measles is characterized by very specific symptoms. In addition this peak is more narrow than the standard bacterial bulges. Its interpretation remains an open question.

Discussion

The investigation conducted in this paper is what can be called a natural experiment in the sense that we studied historical demographic data not at all for historical purposes but because they allowed us to observe the response of newborns and children to pathogens in a time when (i) antibiotics were not known, (ii) vaccines were not used for the diseases under consideration, (iii) the prevalence of pathogens was much higher than it is nowadays. The combined effect of these factors produced fairly high mortality rates which in turn made our observations more accurate.

What can be the usefulness of the kind of measurements performed in this paper?

[2] If the death data in different years can be considered as belonging to a Gaussian distribution these error bounds correspond to a confidence probability of 0.67. Error bars twice as long would correspond to a confidence probability of 0.95. For the "all causes" curves the error bars are so small that they cannot be seen.

Immune system

As already mentioned they may give us an insight into the process by which an autonomous immune system comes about. The broad bacterial peak is probably in relation with the transition from immunity based on maternal antibodies to an autonomous immune system. As a proof of the effectiveness of these antibodies, Moreina et al. (2007) mention the fact that babies with agammaglobulinemia (a deficiency in the production of antibodies) are nevertheless well protected against bacterial infection up to the age of 6 months. Then, maternal antibodies wane over the period of 6 to 12 months.

A macrobiological view

In a broader way such measurements can be seen as giving a "macrobiological" view which may complement the microbiological views from molecular biology. Here we understand the words macro and micro in the same way as in physics. For instance, Boyle's law for the compression of gases is a macroscopic law which can be given a microscopic interpretation via a statistical analysis of the microscopic behaviour of individual molecules. But for other macroscopic laws the microscopic interpretation may be quite involved. The apparently simple Snell-Descartes law for the refraction of light in a transparent medium is, to the best of our knowledge one such example[3]. Ohm's law (traditionally denoted as $V = RI$) for the flow of electricity is another phenomenon that may not be easy to discover when investigated from a purely microscopic perspective. A key objective of our paper is to suggest that in the manner of physics it may perhaps be profitable to revive interest in the search of macrobiological regularities.

Finally, it can be noted that the methodology used in this paper can be extended to study the response function to other exogenous shocks. For instance, it is well known that summertime temperature hikes trigger excess mortality. It is usually assumed that elderly persons are the most severely impacted but this conclusion is not borne out by the age-specific death rate given in a recent study (Vicedo-Cabrera et al. 2016).

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[3]It can of course be derived from Maxwell's equations describing the wave behavior of light but these equations are a macroscopic description too. A real microscopic interpretation should permit to express the refraction index in terms of the parameters defining the molecule-molecule and molecule-photon interactions. An analysis which meets partially this objective was given by Richard Feynman (Feynman et al. 1964, ch. 31). However it is not completely microscopic in the sense that the natural oscillation frequencies of the electrons must be plugged in as macroscopic parameters. A genuine microscopic explanation must be able to account for the absorption and re-emission of photons by atoms and therefore must be based on quantum field theory.

References

Berrut (S.), Pouillard (V.), Richmond (P.), Roehner (B.M.) 2016: Deciphering infant mortality. Physica A 463,400-426.
[The initial version of this paper is available on the arXiv website at the following address: https://arxiv.org/abs/1603.04007]

Berrut (S.), Richmond (P.), Roehner (B.M.) 2017: Age spectrometry of infant death rates as a probe of immunity: identification of two peaks due to viral and bacterial diseases respectively.
[Submitted for publication. An earlier version of the paper is available on the arXiv website at the following address: https://arxiv.org/abs/1610.02198]

Bureau of the Census 1900–1936-: Mortality statistics. In 1937 the series was integrated into a broader publication entitled “Vital Statistics of the United States”.
The whole series is available on Internet at the following address (the subtitle is “underlying causes of death”): https://wonder.cdc.gov/ucd-icd10.html

Bureau of the Census 1915–1936: Birth, stillbirth, and infant mortality. In 1937 the series was integrated into a broader publication entitled “Vital Statistics of the United States”.
The birth volumes are available on the website of the CDC given above but only from 1931 to 1936.

Feynman (R.), Leighton (R.B.), Sands (M.) 1964: The Feynman Lectures on Physics. Vol. 1. AddisonWesley.
[In 2013 the three volumes were made freely available on the website http://feynmanlectures.

Gompertz (B.) 1825: On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Philosophical Transactions of the Royal Society 115,513585.

Kovacks-Nolan (J.), Mine (Y.) 2012: Egg yolk antibodies for passive immunity. Annual Review of Food Science and Technology, 3,163-182.

Moreina (B.), Blomqvist (G.), Hu (K.) 2007: Immune responsiveness in the neonatal period. Journal of Comparative Pathology 137,S27.

Niewiesk (S.) 2014: Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Frontiers in Immunology 5,446.

Sas (A.A.), Snieder (H.), Korf (J.) 2012: Gompertz survivorship law as an intrinsic principle of aging. Medical Hypothesis 78,659-663.

Tsagris (V.), Nika (A.), Kyriakou (D.), Kapetanakis (I.), Harahousou (E.), Stripeli (H.), Tsolia (M.) 2012: Influenza A/H1N1/2009 outbreak in a neonatal intensive care unit. Journal of Hospital Infection 81,36-40.

Vicedo-Cabrera (A.), Ragettli (M.), Schindler (C.), Röösli (M.) 2016: Excess mortality during the warm summer of 2015 in Switzerland. Swiss Medical Weekly 5 December 2016.

Wilkinson (D.J.), Buttery (J.P.), Andersen (C.C.) 2006: Influenza in the neonatal intensive care unit. Journal of Perinatology 26,772776