The Effect of Antibiotics on Mortality From Infectious Diseases In Sweden and Finland

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Abstract: A study was carried out to determine whether the preexisting decline in mortality rates from infectious diseases accelerated after the introduction of antibiotic and chemotherapeutic drugs. Linear regression curves showed that in Sweden mortality rates declined faster in septicemia, syphilis, and non-meningococcal meningitis after the introduction of these drugs. By contrast, for the ten other infectious diseases studied, (scarlet fever, erysipelas, acute rheumatic fever, puerperal sepsis, meningococcal infection, bronchitis, pneumonia, tuberculosis, typhoid fever, and acute gastroenteritis) no such accelerated decline in mortality could be detected. The findings suggest that antibiotic and chemotherapeutic drugs have not had the dramatic effect on the mortality of infectious diseases popularly attributed to them. (Am. J. Public Health 66:1180–1184, 1976)

Introduction

In developed countries mortality from infectious diseases has been replaced as the leading cause of death by chronic degenerative diseases, high mortality among young people has diminished, and life expectancy has improved. To account for this change better hygiene and better resistance to infectious diseases, both associated with higher standards of living, have been suggested.[1] Other authors, however, claim that antibiotic and chemotherapeutic drugs (hereafter referred to collectively as *antibiotics*) have made the major contribution to the decrease in mortality from infectious diseases.[2] However, Chain's data[2] are not conclusive, and that collected in the United States from 1900 to 1970[3] showed no striking change when antibiotics were introduced.

In this study we assess the effect of antibiotics on the death rates for selected infectious diseases in Sweden and Finland, countries which have reliable statistics on causes of death. Sweden has not been involved in wars in this century, so mortality related to wartime does not complicate the analysis. In Finland, where age-standardization coefficients were readily available, the effect of age-standardization could be studied.

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Material and Methods

The total numbers of deaths for 13 selected infectious diseases (listed in Appendix) were taken from Swedish official statistics[4] for the years 1911–1970. These diseases were chosen because: 1) they were important causes of death at the beginning of the century; 2) relatively reliable data on them were available for a long enough time; 3) antibiotics have been thought to be important in reducing mortality from them.

Death rates were calculated by dividing the total number of deaths by the mid-year population in each year and expressed per 100,000 of population. Puerperal sepsis rates were expressed per 10,000 live births. The mid-year populations and the number of live births were obtained from official statistics.[5, 6]

In Finland, only data on scarlet fever, septicemia, pneumonia, tuberculosis and typhoid fever were available for a long enough period (1927 or earlier).* The numbers of deaths (five-year age groups) were collected for these five diseases.[7–9] Figures for infant mortality (deaths under one year of age per 1,000 live births), and for mortality in age group 0–4 years (per 1,000 population) were also calculated for Finland.

To measure the effect of antibiotics, linear regression curves (of form $y = a + b\,x$) were calculated for each disease before and after the introduction of antibiotics. The use

*Since 1936 the classification of causes of death has been the same as the Swedish classification.

of regression curves was based on the assumption that if antibiotics had notably decreased the death rates, their introduction should have changed the trends of the death rate curves. The limitations of this assumption will be discussed later. In most cases, the computation of regression lines was started from 1911. In the case of erysipelas, septicemia, and puerperal sepsis computation was started from 1930. These three diseases displayed a peak of mortality in 1930 and before that an extensive fluctuation in the mortality. At the end of the curve if the death rate remained low and unchanged, the calculation was stopped after four similar figures.

Nineteen thirty-nine was chosen as the year in which sulfonamides were introduced into Finnish and Swedish medical practice. In the case of scarlet fever and acute rheumatic fever introductory year for penicillin, 1947, was chosen as the pivot, as some Finnish authorities did not believe that sulfonamides were effective in treating these conditions.[10, 11] In the case of typhoid fever and tuberculosis, 1950 was chosen since chloramphenicol and para-amino-salicylic acid (the first antituberculotic drug in clinical use in Finland) were introduced in this year. These pivotal years were selected after considering when the drugs were invented, when they came into clinical use,[12, 13] when they started to be imported in Finland,** and when they appeared in articles about infectious diseases in the Finnish medical journal *Duodecim*.

In addition to changes in death rates, the fatality rate for typhoid fever in Finland was analyzed using the notifications made by doctors to the National Board of Health[14, 15] as the denominator. We assumed that the relative frequency of reporting and underreporting remained constant over the years. Such notifications were considered less reliable for other infectious diseases.

Age Standardization

Because the population structure has been changing since the beginning of the century, and because some of the infectious diseases occur predominantly at certain ages, age-standardized death rates were calculated for the Finnish data, standardizing population and age structure to year 1950.‡

The regression lines were calculated for both the age-standardized and the crude populations. The directions of the lines were almost identical in tuberculosis, scarlet fever, and septicemia. In pneumonia, age-standardization changed the directions of the lines somewhat, but not enough to change the interpretation. If the population at ages with the greatest incidence of death differs greatly from the standard year, age-standardization can change the direction of curves. For example, deaths from pneumonia used to occur particularly in infants, whose numbers have decreased since the early 20th century. On the other hand, tuberculosis had a high incidence in young adults, whose numbers have remained fairly constant during the first half of the present century.

Results

Mortality in Sweden

The Swedish mortality rates are given in Table 1 as the mean values of 5-year-periods. For each disease, curves describing the mortality rates were drawn and the regression lines plotted. The curves for septicemia, pneumonia, tuberculosis, and typhoid fever are shown as examples in Figures 1–4. For other diseases,‡‡ only the slopes of the regression lines are given in Table 2. The regression coefficients (b_1, b_2) were computed from the annual data. When b_2 is more negative than b_1, the decline of mortality rates has been more rapid after the introduction of antibiotics. For scarlet fever and typhoid fever (Figure 4) no regression lines could be plotted, since the mortality had already become very low before the introduction of antibiotics.

Table 2 shows that mortality rates declined faster for septicemia (Figure 1), syphilis, and non-meningococcal meningitis after the introduction of antibiotics; for erysipelas, acute rheumatic fever, meningococcal infection, pneumonia, pneumonia + bronchitis (Figure 2), tuberculosis (Figure 3), and acute gastroenteritis no accelerated decline in mortality could be detected.

Mortality in puerperal sepsis and pneumonia + bronchitis (Figure 2) dropped sharply coincident with the introduction of antibiotics, but this is not reflected in the slopes of the regression lines. In puerperal sepsis the slope lines are parallel to each other; in pneumonia + bronchitis the mortality transiently declines and later turns upwards.

Mortality in Finland

The analysis of mortality trends in Finland is more limited. The country was involved in World War II and it is difficult to separate recovery from the war from other factors affecting mortality. Among the diseases with available long-term mortality data, pneumonia and septicemia showed an additional decline in mortality after sulfonamides were introduced, but tuberculosis mortality decline did not accelerate after the introduction of para-amino-salicylic-acid. The findings for septicemia and tuberculosis were similar to the Swedish data.

Finnish infant mortality rates displayed no notable changes using regression lines for years 1911–38 and 1939–70 or alternatively for years 1911–46 and 1947–70. Nor did the mortality rates of the 0–4 year olds change after the introduction of antibiotics. The decline in the fatality rates of typhoid fever appeared to be slightly more rapid after 1950.

**Kytömäki, H., The Association of Finnish Pharmacies. Personal communication, January 1975.

‡For the years 1911–1964, the standardization coefficients were readily available.[16] Standardization coefficient = the mid-year number of people in a specific age-group in 1950 divided by the mid-year number of the same age-group in the year to be standardized. For later years the coefficients were counted from the mid-year-populations by age. The hypothetical numbers of deaths were obtained by multiplying the numbers of deaths by these coefficients. The numbers of hypothetical deaths were counted per mid-year populations of 1950.

‡‡The data for other diseases corresponding to Figures 1–4 are available from the authors.

TABLE 1—Mortality Rates for Selected Infectious Diseases in Sweden, 1911–1970.*

Disease	1911-	1916-	1921-	1926-	1931-	1936-	1941-	1946-	1951-	1956-	1961-	1966-1970
Scarlet fever	4.8	5.6	1.4	1.1	0.82	1.6	0.96	0.12	0.02	0	0	0.02
Erysipelas	4.4	4.3	3.1	5.2	3.6	2.2	0.81	0.31	0.16	0.09	0.06	0.02
Acute rheumatic fever	-	-	-	-	1.0	0.71	0.56	0.27	0.59	0.25	0.09	0.06
Septicemia	10.0	10.6	9.7	14.6	13.7	11.3	6.8	3.3	0.62	0.62	0.66	0.86
Puerperal sepsis	106.7	129.1	113.2	171.3	167.1	115.9	45.1	6.5	6.3	3.4	0.5	1.4
Syphilis	1.4	2.0	1.7	1.4	1.4	1.2	1.0	0.78	0.92	0.45	0.42	0.23
Meningococcal infection	2.8	2.2	1.0	1.3	0.56	0.40	0.37	0.10	0.09	0.12	0.23	0.24
Meningitis	2.2	2.1	2.1	2.2	2.9	3.8	4.0	2.9	1.1	0.96	0.77	0.75
Pneumonia	97.0	94.7	69.1	74.6	83.7	86.8	56.0	40.6	39.4	43.7	45.2	51.1
Bronchitis	23.7	20.5	14.9	11.4	4.7	4.8	3.3	1.9	1.5	1.5	1.7	1.6
Tuberculosis	193.8	181.0	148.5	131.5	108.6	81.5	69.5	39.6	15.6	8.3	5.5	4.4
Typhoid fever et al.	3.9	5.1	2.0	0.94	0.71	0.49	0.37	0.29	0.35	0.057	0.055	0.030
Acute gastroenteritis	31.1	22.2	16.1	12.2	5.9	4.2	3.2	2.2	2.8	3.0	3.9	3.7

*Mean rates for 5-year periods per 10^5 population for all diseases except puerperal sepsis where rate is expressed per 10^4 live births.

TABLE 2—Slopes of Regression Lines Describing Swedish Mortality Rates for Selected Infectious Diseases.*

Diseases	b_1	b_2
Erysipelas (1930-38, 1939-53)	−0.28	−0.085
Acute rheumatic fever (1931-46, 1947-68)	−0.47	−0.23
Septicemia (1930-38, 1939-55)	−0.35	−0.60
Puerperal sepsis (1930-38, 1939-51)	−7.7	−7.0
Syphilis (1911-38, 1939-70)	−0.13	−0.32
Meningococcal infection (1911-38, 1939-51)	−0.86	−0.23
Meningitis (1911-38, 1939-70)	0.52	−1.3
Pneumonia (1911-38, 1939-68)	−0.39	−0.37
Bronchitis + pneumonia (1911-38, 1939-68)	−1.2	−0.45
Tuberculosis (1911-1949, 1950-70)	−4.4	−0.80
Acute gastroenteritis (1911-38, 1939-68)	−1.1	0.039

*The years used for computing the regression lines are shown in parentheses after each disease. b_1 = slope before antibiotics, b_2 = slope after antibiotics.

Discussion

The method used in this study has its limitations, both in principle and in technique. Regression curves are affected by sporadic high and low peaks and by the selection of the starting and ending points. In some diseases, great fluctuations were found especially in the first decades of the century. They may be due to epidemics, or changes in diagnostic habits and classification systems. If the calculation is started at a peak value, the resulting regression curve is not linear with the curve started at an end of an epidemic. It is difficult to draw conclusions if the regression curves are strongly influenced by the selection of the observation period. In this respect the data on scarlet fever, tuberculosis (Figure 3), typhoid fever (Figure 4), and acute gastroenteritis appear to be most reliable. None of these showed an additional decline in death rates after the introduction of antibiotic drugs. The dis-

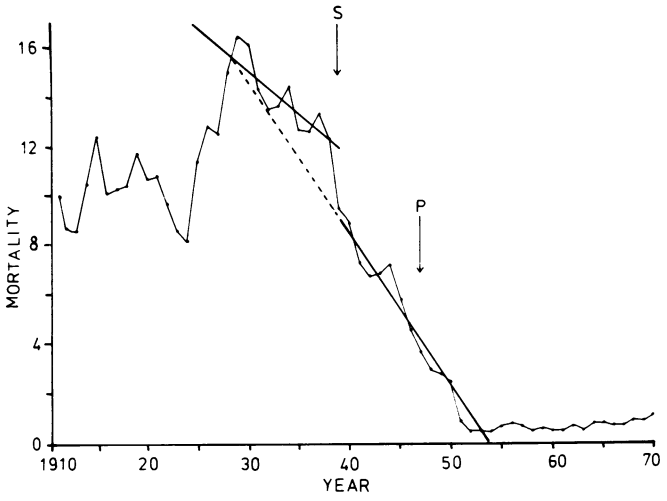

FIGURE 1—Septicemia Mortality Rates per 10^5 Population in Sweden, 1911–70. The Regression Curves are Calculated for the Years 1930–38 and 1939–55

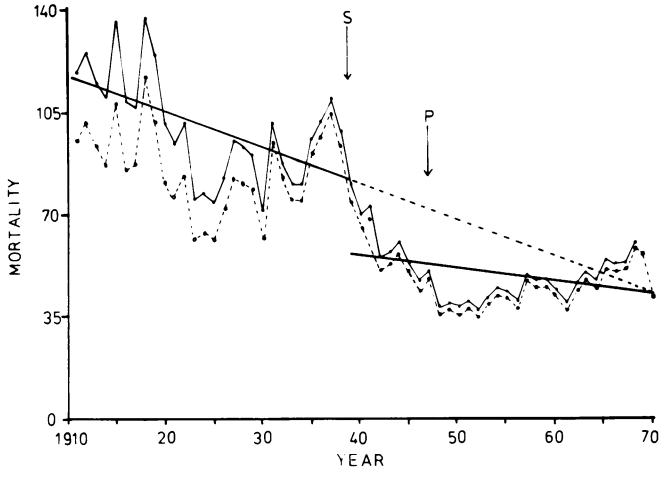

FIGURE 2—Pneumonia + Bronchitis (Solid Line) and Pneumonia (Dotted Line), Mortality Rates per 10^5 Population in Sweden, 1911–68 (70). The Regression Curves of Pneumonia + Bronchitis are Calculated for the years 1911–38 and 1939–68

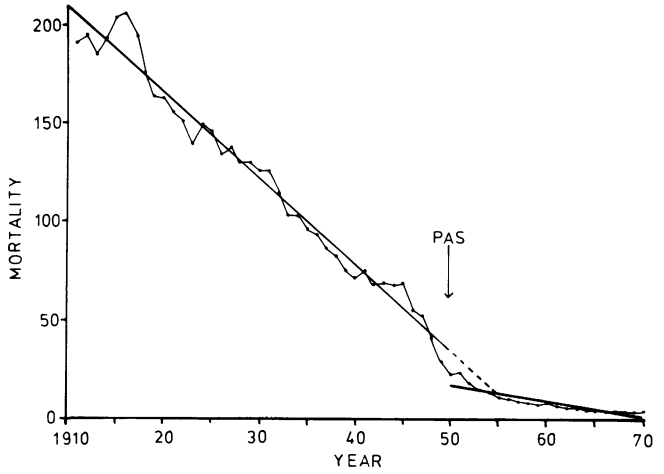

FIGURE 3—Tuberculosis, Mortality Rates per 10^5 Population in Sweden, 1911–70. The Regression Curves are Calculated for the Years 1911–49 and 1950–70. The PAS-arrow Shows the Year of the Introduction of Para-amino-salicylic-acid

turbing influence of epidemics can be partly eliminated by calculating case fatality rates. The unreliability of the incidence figures for non-fatal cases, however, introduces a new source of error. In this study, the case fatality rates could be calculated for typhoid fever in Finland. The decline in the case fatality rate was slightly accelerated after the introduction of chloramphenicol.

A second source of error is introduced by changes in diagnostic habits and classification in the course of time. This problem is less important for infectious diseases than for other diseases. However, the curves for septicemia (Figure 1) and puerperal sepsis suggest that diagnosis became more accurate in the mid 1920s, although the possibility remains that the rise in mortality was real, perhaps attributable to the economic depression.

Thirdly, it is difficult to define exactly when antibiotic drugs were introduced and the contemporary indications for their use. The years when the drugs were well established in clinical use in Sweden and in Finland differ from the years when they were invented. More accurate definition would require data on antibiotic drug sales which are not available.

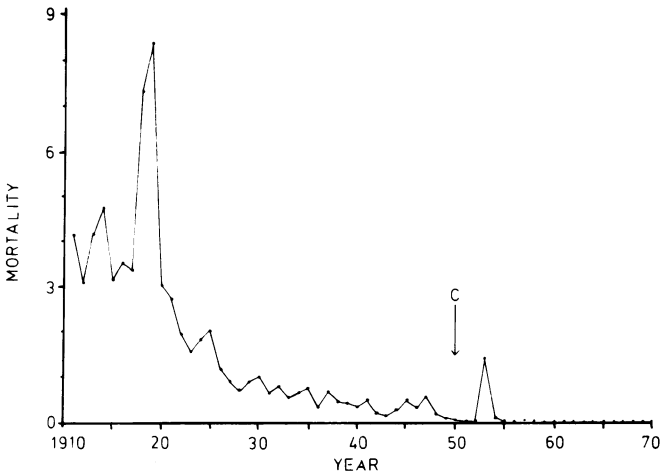

FIGURE 4—Typhoid Fever + Paratyphoid and Salmonellosis et alia, Mortality Rates per 10^5 Population in Sweden in 1911–70. The C-arrow Shows the Year of the Introduction of Chloramphenicol

Fourthly, the method assumes that if antibiotic drugs had not been introduced, the death curves would have remained unchanged, an assumption which cannot be verified. It is possible that without antibiotic drugs, the decline in mortality could have petered out, or that mortality could have risen. In theory at least it is also possible that, without antibiotic drugs, the decline would have been faster.

In the fifth place, the total death rates rather than age-specific death rates were used for most of the analyses reported. It is possible that because of the antibiotic drugs deaths in younger age groups have decreased but that this decrease is obscured by increased deaths among older people, whose general health may be worse than that of older people at the beginning of the century. This kind of shift cannot be abolished by age-standardization. Opposite trends among the young and the old might be anticipated for pneumonia and tuberculosis. Yet age-specific mortality figures from Sweden show that tuberculosis mortality decreased evenly in all age groups, even though the trends were more pronounced in young age groups.[17] In Finland mortality for tuberculosis has increased only in the oldest age group (70–79 years old).[18] No marked changes in curves describing the death rates from tuberculosis and pneumonia in England and Wales can be found after the introduction of antibiotics in the given young age groups, if the figures of the original article[19] which are of logarithmic scales are changed into arithmetic scales. Additionally, the effect of antibiotics did not seem remarkable in diseases which cause deaths mainly within a certain age group (e.g. scarlet fever), for the infant mortality, and the mortality of the 0–4 years old. McKeown and Lowe[20] have reported that sulfonamides had no marked effect on the mean annual death rates for children under 15 years for scarlet fever in England and Wales.

The sixth limitation is that fatal complications might have been reduced by antibiotic drugs, a fact which goes unnoticed if the complications are included in a different class of death.

Finally, the introduction of antibiotics may have had negligible results in Sweden and Finland, despite their potential effectiveness, for the following reasons: 1) ill people failed to consult a doctor, or consulted too late; 2) antibiotic drugs were not ordered adequately, 3) patients did not take the drugs prescribed.

There are many other factors besides antibiotics, (such as changes in the virulence of bacteria, or in the resistance of patients, new methods of caring for and curing disease that do not involve antibiotics, etc.), which can affect death rates from infectious diseases. Mass immunization is of no critical importance for the diseases analyzed, with the possible exception of tuberculosis (immunizations initiated in the late 1930s).

Because of these various limitations, no firm conclusion can be drawn from these analyses. However, the results suggest that the antibiotic drugs did not accelerate the decline in

infectious diseases to any significant extent and that antibiotics have not had the "dramatic" effect popularly attributable to them. Such a notion may have arisen because only short periods of time have been inspected, overlooking the fact that mortality rates were decreasing long before the antibiotic drugs appeared. The frequent use of a logarithmic scale adds to this illusion.[1, 19] The fact that antibiotic drugs do hasten recovery and relieve disease may have been extrapolated to the belief that they also reduced death rates.

Stewart,[21] after comparing the effects on life expectancy of different variables in all nations in the Western Hemisphere, concluded that both literacy and potable water were highly significant, whereas none of the treatment variables were significantly related to life expectancy. McDermott, Deuschle, and Barnett[22] examined the impact of "good" medical care on the health of a rural community of American Indians. They found that in the absence of other social and environmental changes, technological medical care alone had very little effect on many of the indices of health examined. Porter[23] reported that if the commonest infectious diseases of childhood—scarlet fever, diphtheria, whooping cough, and measles—are added together, their combined death rate in England falls steadily from the middle of the last century. Only a small inflection near the end marks the introduction of immunization and antibiotics. The results of this study emphasize the importance of further inquiries into the reasons for the improved health and for the decreased death rates in developed countries.

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APPENDIX

The International Classification of Diseases was revised several times during the period 1911–1970. Only those years are given below, when the classification of infectious diseases has changed. After each selected infectious disease, the year of revision and the contemporary classification rubric is given in parenthesis; the year is italicized for a particularly important change in the classification of the disease specified.

1. Scarlet fever (1911:16, 1931:1090, 1951:A17, 1969:A17)
2. Erysipelas (1911:13, 1931:1210, 1951:A19, 1969:A18)
3. Acute rheumatic fever (1931:1200, 1951:A79, 1969:A80)
4. Septicemia (1911:12, 1931:1220, 1951:A20, 1969:038)
5. Puerperal sepsis (1911:10, 1931:5610 + 5620, *1951*:A115–A119)
6. Syphilis (1911:33, 1931:1520 + 1521, *1951*:A6 + 7 + 10, 1969:A37 + 34 + 35)
7. Meningococcal infection (1911:27, 1931:1250, *1951*:A23, 1969:A19)
8. Meningitis (1911:53, *1931*:2610, *1951*:A71, 1969:72)
9. Bronchitis (1911:67, 1931:3500, 1951:A92)
10. Pneumonia (1911:69, 1931:3520 + 3530, 1951:A81–A91, 1969:A91–92)
11. Tuberculosis (1911:29, 1931:1400–1470, 1951:A1–5, 1969:A6–10)
12. Typhoid fever + paratyphoid and salmonellosis alia (1911:21 + 22, 1931:1000 + 1010, 1951:A12 + 13, 1969:A2 + 3)
13. Acute gastroenteritis (1911:72, 1931:1150, 1951:A104).