Studies in the history of probability and statistics: Semmelweis and childbed fever.
A statistical analysis 147 years later.

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Summary

Semmelweis saved the lives of many mothers and babies by his observation that doctors and medical students who had previously autopsied deceased mothers transmitted cadaveric particles to mothers during childbirth. Beginning in May 1847, doctors and medical students were required to wash their hands in chlorine solution, and the monthly mortality decreased from approximately 10% to about 3%. By simple observation of the monthly mortality rates before June 1847 and after hand cleaning was implemented, Semmelweis concluded that his hypothesis had been confirmed. In this study, the mortality data is analyzed using modern Bayesian techniques based on a shift-point model for mortality.

Some key words: Semmelweis, childbed fever, numerical method, and shift point model.

1. Introduction

Ignac Semmelweis (1818-1865) was born in Pest, Hungary and began to study law but switched to medicine and graduated in 1844 from the University of Vienna. He began his medical career in obstetrics and midwifery at the world famous Allgemeines

Krankenhaus. There were two obstetric divisions: patients in the first division were examined by doctors and medical students, while midwives attended to the patients in the second division. Semmelweis noticed that the mortality in the first division was three times that of the second division and that the students and doctors who attended the expectant mothers saw them after having just performed autopsies. On the other hand, the midwives of the second division were not inlvolved in autopsies. After his colleague, Kolletschka, had cut him self during an autopsy, Semmelweis noticed that the symptoms of his friend were exactly those of childbed fever. At once he realized that the infection was being transmitted from the doctor to the patient, and that this was the cause of the high mortality rate of the first division. This observation saved countless lives of mothers and their babies. After doctors and students of the first division were required to wash their hands in chlorine solution, the mortality rate of the first division decreased to that of the second.

Semmlelweis used about 60 tables of mortality rates to confirm other competing theories and to confirm his hypothesis that cadeveric particles had been transmitted to the patients, and that his solution of hand cleaning had prevented this mode of transmission. Statistical methods in Europe at this time were mostly based on observations of empirical evidence, such as charts and tables. This technique was the so-called Louis numerical method (Louis, 1836), however, analytical techniques were also beginning to gain favor. For example, Gavarett (1840) earlier had shown how to employ the Poisson version of the law of large numbers to compare therapies. (See Matthews [1995] for a history of the early development of quantitative methods applied to medicine, and Nuland [2003] and Horton [2004] for recent information about the life and times of Semmelweis. Murphy's English translation of Semmelweis (1941) is also an invaluable source.)

In this study, a Bayesian analysis based on a Poisson model is used to analyze the monthly mortality data from the first division of the Allgemeines Krankenhaus over a three-year period from January 1846 through December 1848. Adopting non-informative proper priors for the parameters of the model, the posterior distribution of the mortality rates is determined by MCMC resampling methods of the WinBUGS package. A 95% credible interval for the difference in the average mortality rates of the two periods (the first period is from January 1846 to May 1847, while the second is from June 1847 through December 1848) does, indeed, support the hypothesis that cadaveric particles were the cause of childbed fever.

At the time of his discovery, the germ theory of infection was unknown, nevertheless, Semmelweis's momentous discovery helped prepare the way for its understanding, which was later to be fully explicated by Louis Pasteur.

2. Semmelweis and childbed fever: The evidence

In 1861, Semmelweis (see 1941 translation) wrote *The Etiology, The Concept, and the Prophlaxis of Childbed Fever*. Table 1, below, is based on page 356 of the book, where Semmelweis noticed the large difference in annual mortality (for the years 1841-1846) between the patients in the first and second divisions. For the first, the annual mortality was 9.9 % compared to 3.3% for the second.

Table 1. Annual mortality before intervention

	First Division			Second Division		
Year	Births	Deaths	%	Births	Deaths	%
1841	3036	237	7.7	2442	86	3.5
1842	3287	518	15.8	2659	202	7.5
1843	3060	274	8.9	2739	169	5.9
1844	3157	260	8.2	2956	68	2.3
1845	3492	241	6.8	3241	66	2.03
1846	4010	459	11.4	3754	105	2.7
Total	20042	1989	9.92	17.791	691	3.38

According to Semmelweis (page 356), "The mortality in the First Division, since it was devoted exclusively to the instruction of the accoucheurs, remained constant until June 1847; in 1846 it became five times greater, and for a period of six years, on the average three times greater than in the Second Division, in which pupil midwives only were taught, as Table I shows." There were many theories about the etiology of childbed fever, including endemic and epidemic influences, prolonged first stage labor, and the overcrowding of expectant mothers in the First Division. Because of the availability of hospital mortality statistics of the two divisions, over a period of some thirty years, Semmelweis constructed some 60 tables and used them to deftly refute the various etiological theories.

For example, with regard to the overcrowding theory, he points out that the second division had more overcrowding than the first. Also he notes that if overcrowding is indeed a factor in mortality, as the number of births decrease, so should the mortality rate. In Table 2 below, constructed from Table IV of Semmelweis (1941, page 365), the numbers of monthly births in the first division are ordered from largest to smallest.

Table 2. Association between births and mortality

Month	Year	Births	Deaths	%	Fewer Births	More Deaths
Jan	1846	336	45	13.39		
Apr	1847	312	57	18.27	24	12
Mar	1846	311	48	15.43	25	3
Jan	1842	307	64	20.84	29	19
Feb	1846	293	53	18.08	43	8
Mar	1844	276	47	17.03	60	2
Jan	1843	272	52	19.11	64	7
Apr	1846	253	48	18.97	83	3
Oct	1842	242	71	29.33	94	26
Dec	1842	239	75	31.28	97	30
Nov	1841	235	53	22.55	101	8
July	1842	231	48	20.79	105	3
Aug	1842	216	55	25.46	120	10
Nov	1842	209	48	22.96	127	3

There does not appear to be any discernible decrease in the percentage of mortality. Semmelweis was using these tables to show a lack of association between the number of births and the mortality rate. Today we would probably compute the Pearson correlation coefficient as -.710 ($P < .05$) or the Kendall tau b coefficient as -.560 ($P < .05$). This shows that there is a negative association between the number of births and mortality—that is, as the number of births increase, there is a tendency for the mortality rate to decrease. This evidence would indeed not support the overcrowding theory!

The discovery of the true cause of childbed fever makes for fascinating reading, thus we quote Semmelweis (page 391): "On March 20 of the same year, a few hours after my return to Vienna, with rejuvenated spirits I took over again the post of Assistant Physician in the First Obstetrical Division, but was soon overwhelmed by the sad news that Professor Kolletschka, whom I revered highly, had died during my absence. The history of his illness is as follows: Kolletschka, Professor of Forensic Medicine, frequently participated with his pupils, in the performance of medico-legal autopsies; during such an exercise, he was stuck in a finger by a student with a knife which was used during the post-mortem, in which finger I do not recall. Professor Kolletschka then soon became ill with lymphangitis and phelibitis in the same upper extremity and died, during my absence in Vienna, of a bilateral pleuritis, pericarditis, peritonitis, and meningitis, and some days before his death, a metastasis formed in one eye. Still animated by my visit to the Venetian treasure houses of Art, still more agitated by the report of Kolletschka's death, there was forced on my mind with irresistible clarity in the excited state the identity of this disease, of which Kolletschka died, with that from which I had seen so many hundreds puerperae die. The puerperae died likewise of phlebitis, lymphangitis, peritonitis, pleuritis, peracarditis, meningitis, and metastases were also formed in them."

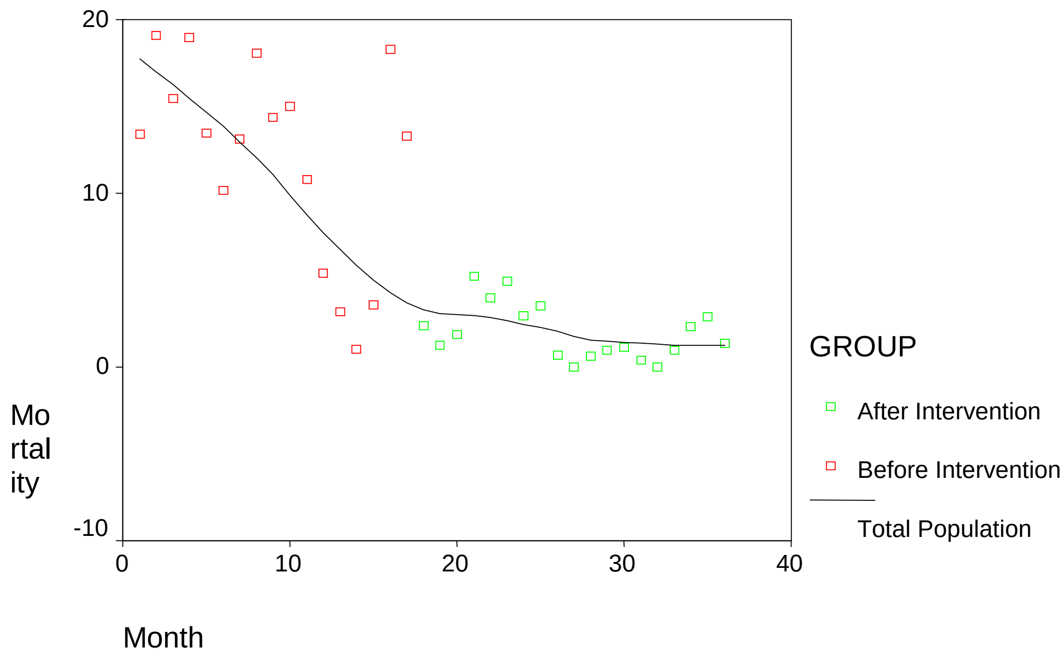
Semmelweis goes on to identify cadeveric material carried by the doctors and medical students from the autopsy room to the expectant mothers of the First Obstetric Division as the cause of childbed fever. Later in support of his conjecture, he used the information from Table 3, below, (see pages 389,393, and 394) of 36 monthly mortality rates covering 1846-1848. The hand washing intervention was introduced sometime in May of 1847, thus the number of months before intervention is 16 and after is 19. Figure

1 depicts the monthly mortality in percent over this three-year period and clearly shows the effect of the intervention on monthly mortality.

Table 3. Monthly mortality before and after intervention

Month	Births	Deaths	% Mortality
January 1846	336	45	13.39
2	293	53	18.08
3	311	48	15.43
4	253	48	18.97
5	305	41	13.44
6	266	27	10.15
7	252	33	13.10
8	216	39	18.05
9	271	39	14.39
10	254	38	14.98
11	297	32	10.77
12	298	16	5.37
13	311	10	3.21
14	312	6	1.00
15	305	11	3.6
16	312	57	18.27
May 1847	294	36	12.24
18	268	6	2.38
19	250	3	1.20
20	264	5	1.89
21	262	12	5.23
22	278	11	3.95
23	246	11	4.97
24	273	8	2.93
25	283	10	3.53
26	291	2	0.68
27	276	0	0
28	305	2	.65
29	313	3	.99
30	264	3	1.13
31	269	1	.37
32	261	0	0
33	312	3	.96
34	299	7	2.34
35	310	9	2.90
December 1848	373	5	1.34

Figure 1. Mortality rate versus month, before and after intervention



During this period, statistical methods were just beginning to be developed for the analysis of medical data, however the use of tables and charts to analyze information was well developed and is illustrated by Semmelweise as follows (page 393).

"In order to destroy the cadaveric particles adhering to the hand, although I cannot recall the date, but about the middle of May 1847, I began to use "Chlorina liquida," with which I and every student were obliged to wash our hands before making an examination. After some time, I abandoned the Chlorina liquida because of its high price and changed to a considerably cheaper chlorinated lime. In May 1847, in the latter half of which the chlorine-washings were introduced, there still died 36 or 12.24% out of 294 puerperae; in the remaining months of 1847, the mortality among the puerperae in the First Clinic was given as follows: [see the above table]. Consequently of the 1841 puerperae cared for during 7 months, 56 died, or 3.04%, when the chlorine-washings were not yet in use, there died 459 puerperae out of 4010 in the First Clinic, or 11.4%. In the Second

Division, 32 died out of 3306 or .9%. In 1848, when the chlorine-washings were used assiduously throughout the year, 45 puerperae died out of 3556, or 1.27%. In the Second Division during this year, 43 died out of the 3219 delivered or 1.33%."

He continues to say, " In 1848, there were two months, March and August, in which not a single puerperal died. In January 1849, there were 403 births and 9 puerperae died, i.e., 2.23%. In February, there were 389 births and 12 puerperae died, 3.08%. March had 406 births and 20 puerperal deaths, or 4.9%."

His main conclusion was stated as follows (page 365): "I have assumed that the cadaveric material adhering to the examining hand of the accoucheur is the cause of the greater mortality in the First Obstetrical Clinic; I have eliminated this factor by the introduction of the chlorine-washings. The result was that the mortality of the First Clinic was confined within the limits of that of the second, as the **above cited figures show.** The conclusion, therefore, that the cadaveric particles adhering to the hand had in reality caused the preponderant mortality in the First Clinic, was also a correct one."

Obvious to Semmelweis, information in Table 3 provided the necessary evidence to strongly support his hypothesis about the transmission of the infection. We now introduce some old and new analytical methods to examine the Semmelweis hypothesis.

3. Statistical Analysis

A. Law of large numbers

During the early part of the 19th century, the comparison of therapies or the effect of interventions was beginning to be tested with the Poisson version (see Stigler, page 187) of the law of large numbers. In his monumental work "Application de la statistique a la medicine," Gavarett (1840) used the law to compare therapies. His interpretation was as follows:

If an event occurred *m* times after a total of *n* trials, then the average *m/n* would vary between limits of oscillation given by

$m/n \pm u\sqrt{2m(n-m)/n^3}$, where the value of *u* determines the probability that the average *m/n* would not vary outside these limits. Gavarett used $u = 2$, the same value chosen by Poisson. We recognize the normal approximation to the binomial, and that when $u = 2$, the probability is .995. Gavarett (see Matthews, page 32) used the Poisson formula for comparing two therapies by the following method:

$$m_1 / n_1 - m_2 / n_2 \pm 2\sqrt{2m_1(n_1 - m_1)/n_1^3 - 2m_2(n_2 - m_2)/n_2^3},$$

where the difference in the two ratios of two independent samples would vary within the limits of oscillation with probability .997. If the observed difference in the two ratios was greater than the limit of oscillation, the probability is .997 that one therapy is superior to the other.

For the Semmelweis data of Table 3,

$m_1 = 579, n_1 = 4886, m_2 = 101, n_2 = 5397$, where the subscript 1 refers to the first 17 months before intervention and the subscript 2 to the postintervention period of 19 months. Since the difference in the two ratios of .0997 exceeds the limit of oscillation .01, the probability is .997 that the intervention is, indeed, effective. The law of large numbers supports the Semmelweis hypothesis that the cause of the infection was the transmission of cadaveric particles from autopsy to the patient.

The language of the period is employed in the above test of hypothesis. At the time, the concepts of null and alternative hypotheses, level of significance, etc. were known, but were to be further developed in the early part of the 20th century. If someone had used the Gavarett approach to test the Semmelweis hypothesis, the above terminology (in French or German) would most likely have been written.

B. A shift-point approach

The Semmelweis hypothesis is that the intervention of hand washing with chlorine solution prevents the transmission of cadaveric material from the caregiver to the patient in the first division, thus reducing mortality to that of the second division. We will test this hypothesis by employing a Bayesian analysis, based on a shift-point model.
For the Bayesian approach to shift-point methodology, see Broemeling and Tsurumi

(1987). The posterior distribution of the difference in the average monthly mortality before and after the intervention will be determined, and the hypothesis tested with the use of a 95% credible interval.

Suppose *Y* is the vector of 36 monthly births and *M* is the vector of 36 monthly deaths, and suppose

M(i) ~ ind Poisson[$\lambda(i)$] , where

$\lambda(i) = \theta_1 * Y(i)$ for i= 1,2,…, k and for i= k+1, …,N(= 36),

$\lambda(i) = \theta_2 * Y(i)$.

k (=17) is the known shift point, and θ_1 and θ_2 are the average monthly mortality rates of the pre- and postintervention periods. The Bayesian analysis required a specification of prior information for the parameters of the model, thus let

θ_i ~ ind gamma(alpha, beta), where

alpha ~ gamma(.01,.01), beta ~ gamma(.01,.01), and k has a probability of 1 of being equal to 17, since we know the intervention was during May 1847. The analysis was executed with WinBUGS, which requires initial values for the parameters of the prior distributions. alpha = beta = 1, and k = 17 were the initial values.

Table 4. Posterior distribution of change in mortality: shift point model

Parameter	Mean	Std Dev	2.5%	97.5%	MC Error
D	.099	.0052	.089	.109	.0000345
θ_1	.118	.0049	.108	.128	.0000308
θ_2	.018	.0018	.015	.022	.0000126

D = $\theta_1 - \theta_2$, the difference in the pre- and postintervention average monthly mortality rates of .118 for the preintervention period, and .018 for the postintervention period. Thus the effect of the intervention is a large 84% reduction in mortality, which of course supports the Semmelweis hypothesis. This hypotheses could be tested by noting that zero is not included in the 95% credible interval (.089, .109) for D.

4. Conclusion

The discovery that childbed fever was being transmitted from the cadavers in the autopsy room to the patients in the First Obstetric Division greatly reduced death at childbirth. Semmelweis creatively employed tables to prove his hypothesis. For example, using tables, he refuted the theory that overcrowding was the primary factor in mortality. Also with the table of 36 monthly mortality rates, 17 before and 19 after intervention, it was obvious to him that chlorine washing had proven his conjecture of the etiology of the disease.

If the law of large numbers had been used in the same fashion as Gavarett had used it, Semmelweis' hypothesis would have been strongly supported by the data. Employing modern techniques, it is seen that a shift-point model, along with a Bayesian approach, would also "prove" the hypothesis.

Much has been written about Semmelweis, and his life was very interesting. At first, he did not publish his findings, but sent letters to various obstetricians throughout Europe, and it was long after he left Vienna for Pest that he wrote *Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebvers*.

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