Public health classic

Epidemiologic investigation of excess maternal and neonatal deaths and evidence-based low-cost public health interventions – Ignaz Semmelweis: the etiology, concept and prophylaxis of child bed fever

S D Gupta

Introduction

*When I look back upon the past, I can only dispel the sadness which fall upon me by gazing into that happy future when the infection will be banished .... The conviction that such a time must inevitably sooner than later arrive will cheer my dying hour.* So wrote Ignaz Semmelweis in his last days while he suffered depression due to continued criticism by medical professionals and colleagues. Semmelweis suggested that simple hand-washing with chlorinated water could prevent the spread of infection and save the lives of women in maternity. His methods showed that maternal deaths due to puerperal fever reduced from 12.2% to 2.4% in maternity wards. He expanded his methods to washing of instruments, which altogether removed puerperal infection in the hospital. However, his observations were in serious conflict with contemporary scientific and medical opinions, which rejected his observations. His suggestion that doctors should wash their hands with chlorinated lime even offended some doctors and his colleagues. They refused to accept that they could be responsible for spreading infection. Semmelweis’s claims were thought to lack scientific basis and his practice of antiseptic use only gained acceptance years after his death, when Louis Pasteur invented the germ theory of disease in 1862, and Joseph Lister invented methods for antiseptic surgery in 1867.

Ignaz Semmelweis’s investigations of maternal and neonatal deaths laid the foundation of modern public health and epidemiological investigations, and prevention of avoidable deaths through hand-washing with chlorine and lime before clinical examination of patients. Semmelweis’s classic approach not only contributed to our knowledge of causal hypothesis, but discovery of appropriate interventions supported by evidence that led to a reduction in maternal and neonatal deaths.

Semmelweis’s insights are a brilliant example of translation of research into action for wider human well-being. Today,
the prevention of puerperal sepsis and infections resulting from deliveries conducted in unhygienic conditions and unsafe abortions is a major approach to reduce maternal and neonatal mortality all over the world. The impact of Semmelweis’s discovery on human health was so immense that millions of maternal deaths have been averted since the initiation of such a simple intervention as the adoption of aseptic procedures during childbirth. Globally, the estimated 526,000 maternal deaths in 1980 are reported to have been reduced to 342,000 in 2008, a reduction of almost one third. Yet a large number of maternal deaths, about 90%, are easily preventable through simple technical and social interventions. Incidentally, 99% of maternal deaths globally occur in developing countries where home deliveries are still common and infection control measures are not adhered to. Puerperal sepsis thus is still prevalent in developing countries and continues to present a significant risk of obstetric morbidity and mortality for women in these regions.

We briefly describe below the investigations of Ignaz Semmelweis and prophylaxis measures that enabled him to demonstrate the significant reduction in maternal and neonatal deaths.

**Study setting**

Semmelweis’s work was based in Vienna General Hospital in 1846 where he worked as an assistant after receiving a degree in medicine with specialization in midwifery, in parallel to studying statistics. The Vienna General Hospital operated two maternity clinics, and was a major centre for midwifery training in Europe, attracting a large number of foreign medical and midwifery students along with the local students.

**Investigations of childbed fever (puerperal fever)**

Semmelweis’s investigation on excess maternal and neonatal deaths is a testimony of modern concepts and approaches of epidemiological investigations. His work demonstrated how simple observations and comparison of frequency of events could help develop causal hypothesis and testing to draw conclusive evidence of cause and effect relationships. He laid the foundation of the modern-day epidemiologic approach: identify and define problem; define research question and develop hypothesis causation and mode of transmission; collect and analyse data; establish cause and effect relationship; develop and design intervention; and evaluate impact.

Semmelweis observed excess maternal deaths among women who gave birth in Vienna Maternity Hospital. Of the two maternity clinics operated by the hospital, he found that maternal deaths were higher in the first. His data collected data on maternal deaths over a period of six years since 1841 showed that, on average, the mortality rate was three times higher in the first clinic over the second clinic. He also noted that the mortality rate was five times higher in the first clinic in 1846 (Table 1).

Semmelweis further observed that the deaths in the first clinic would have been higher as the serious patients were transferred to Vienna General Hospital. When these patients died, they were included in the mortality data of general hospital rather than the first clinic. He also observed that the referral rates of patients in first clinic were higher than the second clinic due to higher frequency of serious patients.

He ascribed these deaths to childbed fever. He defined childbed fever “as a disease
characteristic of and limited to maternity patients, for whose origin the puerperal state and specific causal moments were necessary. He also observed higher mortality among newborns delivered by women and also died in the first clinic due to similar clinical and pathological characteristics (Table 2).

Research questions and hypotheses
The prime research question he had in his mind was why there was higher maternal mortality in the first clinic? What caused excess maternal and newborn deaths? What was the source and how did these women acquire that causative agent?

In order to address his research questions, Semmelweis explored whether the women admitted to the first clinic were different to those in the second clinic (now called selection bias). He reviewed the admission process of the maternity hospital selection bias, if any.

The admission of maternity patients was regulated as follows: Monday afternoon...
at four o’clock admissions began in the first clinic and continued until Tuesday afternoon at four. Admission then began in second clinic and continued until Wednesday afternoon at four o’clock. At that time admissions resumed in the first clinic until Thursday afternoon, etc. On Friday afternoon at four o’clock admissions began in the first clinic and continued through forty-eight hours until Sunday afternoon, at which time again the admissions began in the second clinic. Admissions alternated between two clinics through twenty-four periods, and only once a week did admissions continue in the first clinic for forty-eight hours.

He found that the admissions were done regularly without any predetermined criteria; he concluded that there was no selection bias that would render women admitted to the first clinic more susceptible.

He considered several factors that could possibly be associated with excess maternal deaths in the first clinic, included various clinical conditions, prolonged dilation and other delivery-related characteristics. He also considered environmental factors and the geographic location of the clinics and arrangement of maternity beds in the wards. He found no conclusive difference in maternal deaths.

The authorities were also concerned with disturbing differences in maternal deaths in the two clinics. In order to reduce deaths, several measures were adopted such as transfer of patients to the general hospital, change of physician and medical procedures, environmental conditions and rooms from time to time. Various other measures were also adopted. However, the maternity patients continued to die of childbed fever.

Semmelweis then discovered that mortality was consistently greater in the first clinic since 1940 when it started training only obstetricians, while the second clinic trained only midwives, and wondered whether this could be the reason for the discrepancy. Did obstetricians cause more damage to the birth canal during examination? As most of the physicians were foreigners, it was also posited whether they were rougher than the natives? Incidentally, mortality rates declined when foreigner doctors were excluded from examinations in late 1846 and early 1847; however, they remained higher in the first clinic, and climbed back to higher levels in the months that followed (Figure 1). It did not seem logical that examination by obstetricians, especially foreigners, was associated with higher mortality in the first clinic.

These observations astounded the hospital authorities and Semmelweis. The mystery of higher maternal deaths in the first clinic remained unresolved.

It is interesting to learn how exceptional incidents can play a crucial role in epidemiological investigations of causes and mode of transmission of a disease. Semmelweis left for England to study English in the winter of 1846, returning to Vienna in March 1847. On his return, he learnt that Professor Jakob Kolletschka, who he admired, had died of symptoms similar to those of maternity patients in his clinic. He described his case history as follows:

Kolletschka, Professor of Forensic Medicine, often conducted autopsies for legal purposes in the company of students. During one such exercise, his finger was pricked by a student with same knife that was being used in the autopsy... Professor Kolletschka contracted lymphangitis and phlebitis in the upper extremity... He died of bilateral pleurisy, pericarditis, peritonitis, and meningitis. A few days before he died, a metastasis also formed in
one eye. ... I was haunted by Kolletschka’s disease and was forced to recognize, even more decisively, that the disease from which Kolletschka died was identical to that from which so many maternity patients died.

It proved to be clinching evidence for the cause of childbed fever.

Semmelweis had earlier shown from autopsies that the cause of newborn deaths were identical to those of women who had died from childbed fever, and thus concluded that they died of the same disease. The same results were found in Kolletschka’s autopsy, confirming that he died of the same disease. Semmelweis thus notes:

The exciting cause of Professor Kolletschka’s death was known; it was the wound by autopsy knife that had been contaminated by cadaverous particles ... Kolletschka was not the first to have died in this way. I was forced to admit that if his disease was identical with the disease that killed so many maternity patients, then it must have originated from the same cause that brought it on in Kolletschka.

In Kolletschka, the specific causal factor was cadaverous particles that were introduced into his vascular system. I was compelled to ask whether cadaverous particles had been introduced into vascular systems of those patients whom I had seen die of this identical disease. I was forced to answer affirmatively.

In order to answer yet another important question, i.e. how cadaver particles were transferred to maternity patients, Semmelweis analysed the chain of sequences and circumstances in which these particles could have contaminated the wounds.

The obstetrics students were assigned only to the first clinic and the midwives to the second clinic. The obstetrics students were required to carry out anatomical orientation on cadavers as a part of their training. They washed their hands with soap and water, but this did not destroy the cadaverous particles on their hands. They then examined maternity patients and thus contaminated the genitals of pregnant and delivering patients with cadaverous particles. These particles were
subsequently introduced into the vascular systems of maternity patients, producing a similar disease to that which killed Kolletschka. On the other hand, the trainee midwives in the second clinic were not required to carry out anatomical interventions on cadavers and hence did not visit the mortuary. The assistants, too, in the second clinic seldom visited the mortuary. These observations led Semmelweis to infer that the students whose hands were contaminated with cadaver particles were responsible for transmission of childbed fever.

**Intervention**

History was made. The cause of childbed fever (puerperal sepsis) was discovered which still kills tens of thousands of women during pregnancy and childbirth in developing countries today. Semmelweis went forward to discover an intervention to prevent the spread of the disease. He hypothesized that, if the cadaverous particles are destroyed chemically, the disease must reduce or be prevented. He instituted hand-washing with chlorine solution before examining maternity patients (Figure 1):

*To destroy cadaverous matter adhering to hands, I used Chlorina Liquida. This practice began in middle of May 1847... Both students and I were required to wash (hands) before examinations. After a time I ceased to use Chlorina Liquida because its high price, and I adopted the less expensive chlorinated lime. In May 1847, during the second half of which chlorine washings were first introduced, 36 patients died – this was 12.24 percent of 294 deliveries. In the remaining seven months of 1847, the mortality rate was below that of the second clinic.*

**Monitoring and evaluation of intervention**

Semmelweis evaluated the effect of chlorine washing of hands and equipment, and demonstrated that chlorine prevented the transmission and spread of childbed fever as observed from reduction in mortality rates among maternity patients in the first maternity clinic compared with the mortality levels in the second maternity clinic (Table 3).

*In these seven months, of 1841 maternity patients cared for, 56 died (3.04%). In 1846, before washing with chlorine was introduced, 4010 patients cared for, 459 died (11.4%). In the second clinic in

**Table 3: Annual births, deaths, and mortality rates for all maternity patients at the clinics of the Vienna Maternity Hospital for 1839, 1840, 1846–1948**

<table>
<thead>
<tr>
<th></th>
<th>First clinic</th>
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<th>Rate</th>
<th>Second clinic</th>
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<th>Rate</th>
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<tbody>
<tr>
<td></td>
<td>Year</td>
<td>Births</td>
<td>Deaths</td>
<td>Rate</td>
<td>Births</td>
<td>Deaths</td>
<td>Rate</td>
<td></td>
</tr>
<tr>
<td>Pre-training year</td>
<td>1839</td>
<td>2781</td>
<td>151</td>
<td>5.4</td>
<td>2010</td>
<td>91</td>
<td>4.5</td>
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<tr>
<td>Obstetric training permitted</td>
<td>1840</td>
<td>2789</td>
<td>267</td>
<td>9.6</td>
<td>2073</td>
<td>55</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Before chlorine washing</td>
<td>1846</td>
<td>4010</td>
<td>459</td>
<td>11.4</td>
<td>3754</td>
<td>105</td>
<td>2.8</td>
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<tr>
<td>Chlorine washing introduced</td>
<td>1847</td>
<td>3490</td>
<td>176</td>
<td>5.0</td>
<td>3306</td>
<td>32</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>After chlorine washing</td>
<td>1848</td>
<td>3556</td>
<td>45</td>
<td>1.3</td>
<td>3219</td>
<td>43</td>
<td>1.3</td>
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In 1846, of 3754 patients, 105 died (2.7%). In 1847, when approximately the middle of May I instituted washing with chlorine, in the first clinic of 3490 patients, 176 died (5%). In the second clinic, of 3306 patients 36 died (1%). In 1948, chlorine washings were employed throughout the year and of 3556 patients, 45 died (1.3%). In the second clinic in the year 1948, of 3219 patients 43 died (1.3%).

Replication of interventions
Semmelweis was convinced that hand-washing with chlorinated lime before examining the patient by doctors would reduce maternal and neonatal deaths. He suffered ignominy at the hands of his fellow colleagues and seniors. He left the Vienna hospital as he could no longer endure the frustrations of dealing with the Viennese medical establishment, and returned to Pest in Hungary. Despite being criticized by the medical community and fellow colleagues, Semmelweis replicated his intervention by introducing hand-washing with chlorine water in Pest’s small St Rochus Hospital where childbed fever was rampant. From 1851 to 1855, only eight patients died of childbed fever out of 933 births (0.85%). The results he demonstrated in Vienna Hospital were thus reproducible. He repeated the same interventions in 1857 when he took over as Professor at the University of Pest maternity clinic, where the results were once again impressive.7

Research for action
Research remains impotent unless it is used to protect and improve human health and promote welfare through public health action. Semmelweis’s research is a salient example of how research was employed to improve human health. His observations and experiments formed the basis of modern-day infection control measures in hospitals and health care in general. Infection control measures, especially disinfection of hands and equipment have saved the lives of millions of pregnant and childbearing women who may have died of puerperal sepsis all over the world, thanks to the great discovery of Semmelweis. Hospital infection control is the hallmark of patient safety today.

Semmelweis’s seminal observations led the way for modern epidemiologic thinking and approach. Observations of disease trends and making comparisons are critical components of modern-day epidemiological approaches for initiating investigations and testing causal hypotheses. Semmelweis systematically observed maternal death trends in the maternity hospital and developed a causal hypothesis. Though he could not explain the causal agent, he successfully investigated the source of infection and mode of spread of puerperal fever among women who gave birth in his hospital. He also successfully demonstrated that if the chain of spread was blocked, the disease could be prevented. Nevertheless, Semmelweis could not provide scientific evidence to prove his hypothesis that cadaveric particles produced puerperal fever. He was severely criticized by his contemporary medical professionals and scientists for bruising their ego and for his statements that doctors were responsible for the spread of infection.

Semmelweis was reluctant to publish his work and disseminate the results among the scientific community until 1861 when he published his book on Concepts, Etiology and Prophylaxis of Childbed Fever, 16 years after his discovery. Dissemination of research is critical to create awareness, advocacy and acceptance of its results, in order to further its applications as evidence for policy and action. However, there are several barriers that obstruct meaningful dissemination and uptake of the results. Research evidence is one of many inputs to acceptance and
decision-making by peers, fellow professional groups and clinicians, health-care managers, and health-care policy-makers. Translating research into action requires intellectual rigour, discipline, creativity, clinical judgment and skills, a favourable organizational climate, and above all endurance and tolerance towards contemporary scientific reviews and comments.8–13 Semmelweis was academically brilliant and made a seminal discovery, but lacked leadership skills. He was arrogant, severe on his critics, calling them murderers and medical ‘Neros’, and accused his superiors of causing the deaths of mothers. He became frustrated and angry with himself, but refused to publish his monumental discovery.

He was denied recognition in his lifetime and finished his days in a mental asylum in ignominy, dying at the very young age of 47 years. His work was recognized only after about two decades of his demise with the advent of germ theory and the value of antiseptic techniques in preventing spread of infection. He was described as the saviour of mothers. His discovery of hand-washing with antiseptic solution left a legacy in modern medicine and infection control, thus saving the lives of millions of women; not only averting deaths from nosocomial infections, but reducing the cost of health care the world over. The Austrian Government issued a commemorative 50 euro coin in 2008 in his honour; and libraries, museums and universities have been named Semmelweis in recognition of his discovery and contribution to medical science.

References


