

The Haemophilus Vaccine: A Victory for Immunologic Engineering

by

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Half past three in the afternoon of November 27, 1987, Catherine received a phone call from her mother. She felt a moment of panic. Was Josephine all right? Catherine worked at a day care center and Josephine, her 34-month-old daughter, was minded by Catherine's mother during the day while Catherine was at work.

"You have to come immediately. Josephine is feverish," her mother said. "She is also delirious."

There was no need for Catherine and her mother to say what they both had on their minds. In the day care center in Umeå, Northern Sweden, where Catherine worked two children had developed bacterial meningitis this fall. The first case occurred on September 18th and the second on November 13th. The children were 11 and 21 months old, respectively, and had been hospitalized at the Department of Pediatrics, University Hospital of Umeå. They had both been given an intravenous 10-day course of cefuroxime, an antibiotic related to penicillin although with a broader antimicrobial spectrum. In both cases, *Haemophilus influenzae* had been cultured from a specimen of cerebrospinal fluid.

All of the parents and personnel of the day care center were well aware of the risks associated with bacterial meningitis. In Western countries, the case fatality risk is 2 percent. Among those who survive, 25 percent develop permanent sequelae, 10 percent in the form of sensorineural hearing impairment.

"I'm on my way, Mother. Wrap her in a blanket and meet me at the parking lot in front of your house."

After nearly being involved in an accident at Pig Hills corner, Catherine arrived at her mother's house and from there went with her and Josephine to the hospital. It occurred to Catherine that she had forgotten to check Josephine's condition, probably because she was so anxious to get to the hospital as quickly as possible. In the emergency room, she found Josephine unconscious. She was convinced this must be meningitis and tried to give this information to the nurse immediately.

"Two children at the day care center where I work have recently been diagnosed with bacterial meningitis."

The phone call from the emergency room nurse to the pediatric ward was brief. She only had to mention the name of the day care center and was told to send the patient immediately to the pediatric ward. Within minutes after Josephine was admitted to the pediatric ward, she was injected with cefuroxime and an intravenous line for fluid replacement was started.

Josephine was subjected to a lumbar puncture and a sample of cerebrospinal fluid showed an increased number of leukocytes ($8.2 \times 10^9/L$), most of which were neutrophils ($7.3 \times 10^9/L$), i.e., the cells expected to increase in bacterial infection. This is more than 1000-fold the number of cells found in the cerebrospinal fluid of healthy individuals.

During Josephine's first night in the hospital, Catherine never left her bedside. The next morning, Josephine's temperature was still high ($39.5^\circ C$), but the nurses seemed satisfied with Josephine's improvement overnight. Her blood pressure, heart rate, and eye reflexes had been checked throughout the night.

At this point, Catherine was confused and had several questions. In addition, she anticipated that there might be telephone calls from the day care center and from journalists once the occurrence of three cases of a severe contagious disease in a day care center became known in the community. Hospital personnel felt it was critical that all answers to the media's questions be consistent and medically correct.

Questions for You to Consider

1. What is the pathophysiological role of the leukocytes in the present situation?
2. How sure could you be at this stage, a few hours after admission to the hospital, that Josephine is indeed ill with bacterial meningitis? What other diagnoses might be considered? What bacterial agents other than *H. influenzae* cause meningitis and at what ages? What is the spectrum of illnesses caused by *H. influenzae*? What is the relation between capsular type of *H. influenzae* and pathogenicity?
3. Why did Josephine become ill? Shouldn't her host defense system have stopped the infection from the beginning? Could there be some kind of immunodeficiency? What are your comments on the choice of antibiotic therapy?
4. Catherine received telephone calls from the director at the day care center. The center's staff was deeply worried and wished to know the risks for the remaining children of the center and for other center personnel. What should the Center say to the parents? Should all the children receive preventive treatment? Your advice will be of the utmost importance given that the news media may soon become aware of the present series of cases and a whole region alerted. Prepare a statement (to be shown by overhead projector) to inform parents and the community about the problem.

One day after admission, the hospital laboratory reported growth of *Haemophilus influenzae* in samples of Josephine's cerebrospinal fluid. Her condition improved and within 10 days she was discharged from the hospital. After a convalescence of three weeks, she was ready for outdoor activities and, at her follow-up visit, no sequelae were noted.

A considerable period of time has lapsed since this case occurred. The risk of such an event occurring today at a day care center in Sweden, the United States, or another developed country is very low. During the late 1980s, a novel *Haemophilus* vaccine (Hib vaccine) was developed and shown by extensive trials to protect already within the first year of life. The vaccine has been on the market for several years.

Assignments/Questions

5. Analyze the results from the phase III trials with the *Haemophilus* vaccine (see Peltola et al. 1992 and Garpenholt et al. 1996, which you should read before class). Are there any risks involved in the vaccination procedure? Be prepared to summarize these results in class. During the class discussion, we expect to be paid a visit by a representative of the association "Mother Earth," which is against all kinds of artificial prophylactic approaches. Be prepared to argue.
6. Describe immunological mechanisms underlying the success of conjugation of the vaccine (see Parham 2000, which you should read before class).
7. Do you expect the *Haemophilus* vaccine to protect against epiglottitis and otitis? Explain why or why not.

Literature to be read prior to the case discussion:

Peltola, H., T. Kilpi, and M. Anttila. 1992. Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet* 340:592-4

Garpenholt, Ö., S-A. Silfverdal, S. Hugosson, H. Fredlund, L. Bodin, V. Romanus, and P. Olcén. 1996. The impact of *Haemophilus influenzae* type b vaccination in Sweden. *Scand J Infect Dis* 28:165-9.

Parham, P. *The Immune System*. New York: Garland Publishing/Elsevier Science Ltd., 2000, pp. 154-157.



The image that accompanies this case study is taken from a slide showing a leukocyte about to engulf bacteria. From the *Neutrophils* slide series published by Schering-Plough of Stockholm, Sweden, 1991. Used with permission.

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