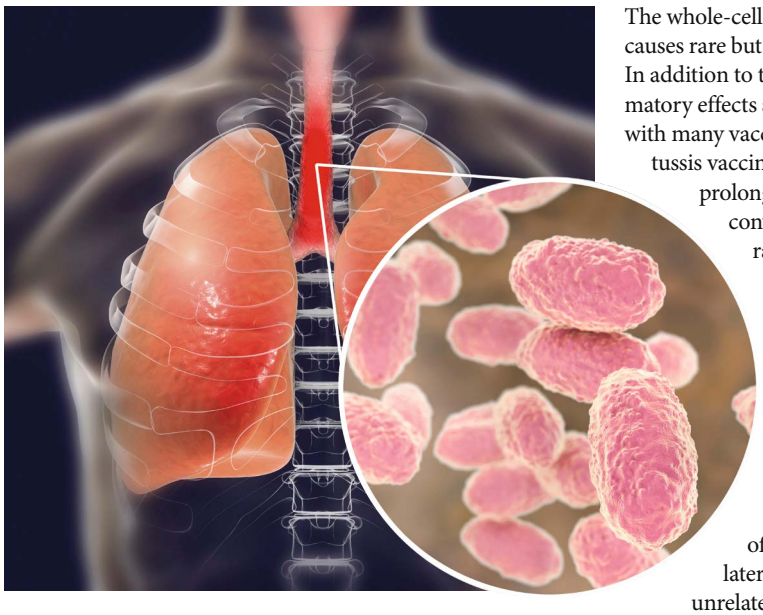
MILESTONE 8

Pertussis: a tale of two vaccines



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Pertussis, or 'whooping cough', has been identified since at least the Middle Ages as a disease that affects mostly infants and children, but can also affect teenagers and adults. The symptoms in the early stages of illness are similar to a cold, and then develop into a characteristic cough accompanied with gasping breaths ('whoops'). It is highly infectious; early 20th-century statistics claimed an average death rate of 10% in children.

A therapeutic vaccine of uncertain efficacy was developed shortly after the discovery of the causative agent, *Bordetella pertussis*, in 1906. However, it was not until 1939 that an effective preventive vaccine was designed. Thanks to improved cultivation methods, Pearl Kendrick, Grace Eldering and Loney Gordon developed a highly effective, whole-cell inactivated vaccine (wP). In the late 1940s the pertussis vaccine was combined with diphtheria and tetanus toxoids to become DTP and was widely adopted shortly afterwards.

By the early 1980s, the introduction of pertussis vaccines was associated with a large decline in cases, with incidence of whooping cough in the USA decreasing 150-fold. Unfortunately, as the risks from whooping cough decreased markedly, attention shifted from the risk of disease to fear of vaccine side effects.

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The whole-cell pertussis vaccine causes rare but significant side effects. In addition to the usual local inflammatory effects and fever associated with many vaccines, whole-cell pertussis vaccines sometimes trigger prolonged crying and febrile convulsions and, very rarely, hypotonic–hyporesponsive episodes. Claims of causal links to various neurological issues were also made. However, those neurological side effects were observed in very small numbers of children and were later demonstrated to be unrelated to the vaccine, but the reputational damage was done.

The whole-cell pertussis vaccine was blamed for causing various intellectual and physical disabilities, including in a TV documentary. This precipitated the formation of 'Dissatisfied Parents Together', which would eventually become the National Vaccine Information Center, and remains to this day a major source of disinformation about vaccines in the USA.

Thousands of parents refused to vaccinate their children, and a flood of personal injury lawsuits forced many companies to stop producing vaccines. The US Congress passed the National Childhood Vaccine Injury Act, to protect vaccine manufacturers, which ironically is now used by vaccine deniers as 'proof' of the dangerous nature of vaccines. Three countries, Sweden, the UK and Japan, interrupted or decreased pertussis vaccination.

Meanwhile, in response to concern about the side effects, Yuji Sato was working on an acellular pertussis vaccine. There had always been resistance to the whole-cell vaccine in Japan, and, persuaded that the side effects were caused by products such as lipopolysaccharide and endotoxins present in the vaccine, he set out to create a less reactogenic vaccine. By 1974 his team had succeeded in producing an effective pertussis vaccine containing mainly just two antigens: pertussis toxin (PT) and filamentous haemagglutinin (FHA). This acellular pertussis vaccine (aP) was shown to be effective, albeit less so than the whole-cell vaccine, and in 1981 was approved for use in Japan. Other countries adopted similar methods of producing acellular vaccines, usually with added pertactin and type 2 and type 3 fimbriae for better effectivity, and combined it to create the diphtheria, tetanus, acellular pertussis vaccine (DTaP). By the late 1990s, most high-income countries had switched to DTaP, although the cheaper DTwP remains the vaccine of choice in low- and middle-income countries.

This could be the end of the story, except that in countries using DTaP there is now a resurgence in cases of whooping cough, with the characteristic peak every 2–5 years that was observed in the pre-vaccine era. There are a number of hypotheses as to why this previously well-controlled disease is now making a resurgence. It has been suggested that the less-effective long-term protection (waning after 5–10 years) of DTaP has allowed the epidemic cycles to re-establish themselves. This is partly challenged by more recent studies that allege a long-lived, if imperfect, protection afforded by DTaP. Understanding of the transmission and contact networks is incomplete, and studies looking at vaccine evasion in *B. pertussis* are not conclusive.

In the meantime, several countries are experimenting with new vaccination schedules and vaccination of pregnant women, and the search for a better vaccine continues.

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