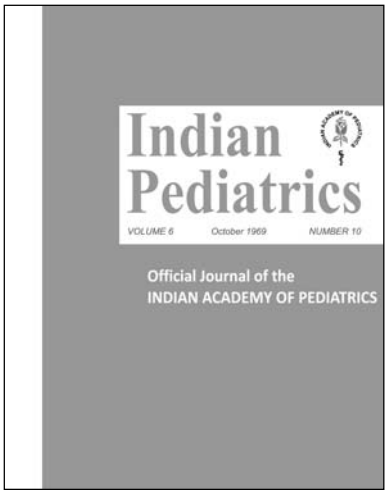
Pertussis: 100-day Disease Over 50 Years!

POOJA DEWAN* **AND DHEERAJ SHAH**
*Department of Pediatrics, University College of Medical Sciences, Delhi, India. *poojadewan@hotmail.com*

The October 1969 issue of *Indian Pediatrics* included some insightful research papers – incidence and severity of whooping cough from Southern India, vital health statistics from a rural township in Maharashtra, kidney functions in protein calorie malnutrition, developmental delay as a diagnostic indictor in cerebral palsy, and the role of some selected antibiotics in treatment of infective diarrhea in children. We decided to review the research paper by Ashabai, *et al*. [1] on whooping cough as it is particularly relevant in the present time when there is zero tolerance for childhood deaths due to vaccine preventable diseases (VPDs). While the study was limited by its small sample size and simplistic methodology, it does provide priceless health statistics from an era when methodological rigor in community-based studies was still in its nascent stage.



THE PAST

The study was a part reporting of results of a survey conducted over three years (1965-1968) from three semi-urban localities of Vellore (Tamil Nadu, India) wherein 100 families were recruited in a random manner [2]. The data were collected using a questionnaire as well as by direct observation by a public health nurse and/or a pediatrician. Whooping cough or pertussis was diagnosed on the basis of clinical assessment and indirect laboratory evidence in the form of lymphocytosis. A total of 207 children aged <10 years were observed during the study period amounting to 622 child-years of observation; of these, 53 children were reported to suffer from pertussis. This translated to an annual incidence of 85 cases per 1000 children aged below 10 years, and 115 cases per 1000 children below 5 years. The median age for pertussis infection was 2.4 years, and by 10 years of age, nearly 60% of the children had suffered from pertussis. Pertussis occurred throughout the year, and September to December seemed to be the peak season. The clinical features included >10 paroxysms of cough, rhinitis, recurrent vomiting, fever, crepitations on chest auscultation, periorbital edema, bleeding (hemoptysis, subconjunctival hemorrhage and epistaxis), defecation with cough, and oral ulcers. The duration of illness ranged from 5 weeks to more than 25 weeks. Most cases had an uneventful recovery while seven developed pneumonia and one had encephalopathy. Infants suffering from pertussis showed marked delay in gaining weight. More than half (57%) of the mothers believed that the disease was a consequence of supernatural powers; only 14% knew about the infective etiology and the awareness on preventive immunization was dismal at 8%.

Historical background and past knowledge: Whooping cough has been known to mankind since the medieval period with anecdotal records from Africa and East Indies; however, the first epidemic of whooping cough in Paris was described scientifically by Guillaume de Baillou in 1578 [3]. Since then, the disease has persisted over the years as a stubborn respiratory illness with prolonged morbidity earning it the name of "100 day cough." In 1679, Thomas Sydenham, an English physician, christened whooping cough as 'pertussis' – meaning a violent cough of any type. It was much later in 1900 that Julius Bordet and Octave Gengou, two Belgian scientists, could identify the causative agent of the illness as a gram-negative coccobacillius in the sputum of a 5-month-old infant suffering from whooping cough [4]. It was after another six years that these two scientists managed to prepare a special Bordet-Gengou (BG) medium to culture this elusive pathogen. The bacterium was in fact first cultured from the sputum of Bordet's own nephew who had contracted whooping cough; the bacterium grew in

greyish-white glistening colonies on the BG medium. While the two failed to develop a successful vaccine to combat this cough microbe, the bacterium was christened in the honor of its discoverer as *Bordetella pertussis*.

It was in 1940s, that the first potent whole-cell vaccine against whooping cough was devised by the trio of Dr. Pearl Kendrick, Dr. Grace Eldering, and Dr. Margaret Pittman [5]. Over the next few years, the use of whole cell pertussis vaccine in combination with diphtheria and tetanus vaccine (DTwP) led to a decline in the number of pertussis cases. However, soon a few cases of fatal neurological complications following DTwP vaccination were reported leading to public uproar and skepticism, and attempts were made to develop safer and less reactogenic acellular pertussis vaccines. Between 1979 and 1981, Sato developed and used the first acellular pertussis vaccine in Japan with claims of lesser chances of febrile seizures and local reactions [6]. Many countries, including USA, abandoned the DTwP vaccine replacing it with the acellular pertussis combined with diphtheria and tetanus (DTaP) vaccine in their national programs. However, due to concerns over the heightened cost of acellular vaccine and possibly the suboptimal efficacy of DTaP vaccine compared to DTwP [7], the DTwP continued to be used in national immunization programs of several countries, including India.

THE PRESENT

Ever since, the introduction of the Expanded Program on Immunization (EPI) by the World Health Organization in 1974, there has been more than 15-fold decline in the incidence of pertussis cases globally. In 1980, about 2 million cases of pertussis were reported globally which declined to 149,089 cases in 2015 [8]. These global trends are reflected in India as well, for it contributes to a staggering 26.7% of world's total cases of pertussis [9]. In 1970, there were 200,932 cases of pertussis in India with 106 deaths attributable to pertussis. With the launch of the Universal Immunization Program in 1985, this figure plummeted to 31,122 in 2005 [9]. The success in capping the number of pertussis cases can be attributed to the improved immunization services across the world. The recent figures from fourth National Family Health Survey (NFHS-4) of Indian show that 74% of children aged 12-23 months in Vellore are fully immunized, and 92.3% of these children have received at least 3 doses of DPT vaccine against national figures of 62% and 78%, respectively [10]. Indeed, we have come a long way since 1969, when Ashabai, *et al*. [1] found that merely 8% mothers amongst the sampled population in Vellore were aware that pertussis is indeed preventable by a vaccine.

Unfortunately, there has been a resurgence of pertussis recently; 174,177 cases of pertussis were reported globally and 37,274 cases from India in 2016 [9]. The reasons for this resurgence can be attributed to greater surveillance and more sensitive diagnostic laboratory tools, including serological tests like ELISA as well as polymerase chain reaction (PCR). Compared to the tedious process of bacterial culture, PCR is faster and more sensitive. However, it is marred by poor specificity and may not differentiate *B. pertussis*, *B. holmesii*, *B. parapertussis*, and *B. bronchiseptica* (all colonize the respiratory tract and cause respiratory problems) unless several target sequences are used for diagnosis. As most commercially available diagnostic PCR assays for pertussis use fewer targets, they are not species-specific [11].

Waning immunity following vaccination with DTaP compared to DTwP has also been proposed as one of reasons for the recent rise in pertussis [12]. In a field study, the odds for acquiring pertussis were shown to increase annually by 42% following the fifth dose of DTaP [13]. Consequently, older children and adolescents were found to be more susceptible to pertussis. Lesser duration of protection following vaccination compared to natural infection along with lower vaccination coverage rates among toddlers and young children in the United States seem to be the reasons behind the resurgence of pertussis [14]. This concern of waning immunity of DTaP vaccine led Indian Academy of Pediatrics (IAP) in 2013 to not recommend acellular pertussis vaccine for primary immunization of infants [15]. However, in 2018-2019, because of the concerns related to parental acceptance of DTwP and possibility of consequent increase in the prevalence of disease, the committee recommended that either DTwP or DTaP can be used for primary immunization [16]. Though only DTwP is still being used in government immunization programs of India, both whole cell and acellular pertussis vaccines are used in private sector, especially as a part of hexavalent combination vaccines [17].

Antigenic shifts in *B. pertussis* and pathogen adaptation has also emerged as a significant issue. The more virulent *ptxP3* strains of *B. pertussis* have been shown to replace the resident *ptxP1* strains. The antigenic shift poses a serious concern as the current vaccines may not produce neutralizing antibodies and effective memory T-helper cells [18]. While, replacing the vaccine strains is a long-drawn project, it may be worthwhile to consider interim strategies like vaccinating adolescents and pregnant mothers with TdaP [15,16] and 'cocooning' to ensure protection of neonates and infants. While these measures are particularly challenging in low-

and middle-income countries including India, a comprehensive approach is need to tackle this re-emerging disease.

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