# Pertussis Outbreaks in the Developed World: Are Acellular Pertussis Vaccines Ineffective?

## THE POINT

Pertussis remains endemic across many countries in the globe inspite of availability of reasonably effective vaccines. The success story of pertussis control by these vaccines has suffered a setback since 2000 when inspite of high vaccine coverage there has been resurgence especially in infants, adolescents and adults. The recently witnessed large scale outbreaks in developed countries has initiated a vigorous debate on the efficacy of vaccines, the immunization schedule and the demographic factors. The outbreaks have been reported from Australia, New Zealand, UK and USA; the most notable and analyzed have been in the Queensland 2009-2011 (Australia), California 2010 and Washington 2012 (USA) [1-6]. The common feature has been the exclusive use of acellular pertussis vaccine in all these places and a peak seen in 7-14 years of age.

## PROBABLE CAUSES OF OUTBREAKS

The outbreaks have been attributed to multiple factors:

1. *Increased awareness* amongst the medical fraternity and the population at large in developed countries has contributed to the higher number being diagnosed [7].

2. *Better diagnostics* like polymerase chain reaction (PCR) have helped diagnosis of mild infections in the immunized and atypical cases. In USA outbreaks, 83.4% were laboratory confirmed: 94.7% by PCR alone as compared to 2.4% by culture and 2.9% by both PCR and culture [5,6]. Overdiagnosis is possible because of false positive PCR. There is a need to standardize multi-targeted PCR which specifically diagnose *B. pertussis* and not other species of genus *Bordetella* like parapertussis, bronchiseptica, holmesii which can have a similar clinical presentation.

3. *Failure to vaccinate*: Endemic pertussis is characterized by regular peaks every 3-5 years and is explainable by the accumulating numbers of unimmunized susceptibles so as to cross the outbreak threshold levels. In California, 75.8% were completely immunized for age (5 doses) by 10 years, and only 43.1% children aged 11-12 years had received Tdap. The figures were similar for Washington [5, 6]. The Queensland outbreak has not been analyzed for the 4$^{th}$ dose at 4 years of age as per the immunization schedule in Australia. The national registry figure is 80% coverage in 2009 and 92% in 2013 at 5 years of age, and has presumably increased after the outbreaks [8]. The outbreaks in Australia could be due to lack of 2$^{nd}$ year booster for DPT vaccine [9].

4. *Failure of the vaccine*: It is a known fact that a well manufactured whole cell vaccine is slightly better than a well manufactured aP vaccine [10]. There is a wide variation in the quality of available DTwP vaccines while aP vaccines are fairly well standardized. The replacement of DTwP vaccines by DTaP has been a fine balance between the modest efficacy and the significantly reduced reactogenecity to overcome the poor acceptance of DTwP vaccines in the era of drastic reduction in the disease pressure. The earlier efficacy estimates of both wP and aP vaccines are likely to be inflated because of the non-comparability of the multitude of studies done in the 80's and 90's as regards the methodology, case definition and diagnosis, different vaccines and population studied [11]. In the last two decades, many developed countries have kept the disease effectively controlled by exclusively using aP vaccines. The real culprit appears to be the secondary vaccine failure due to a differential waning immunity amongst different populations across different regions within the same country for reasons hitherto unknown. This clearly explains the occurrence of staggered outbreaks rather than a countrywide phenomenon. The highly immunized population in developed countries with a low circulation of wild organisms particularly become susceptible in the event of the lack of natural boosters. Thus periodic boosters become all the more important and should be guided by the waning immunity in these specific populations. Though all is

not well with the vaccines, it has easily become a soft target as all the countries reporting outbreaks have exclusive use of aP vaccines. It is however pertinent to note that a recent outbreak was reported in Pakistan where exclusively whole cell vaccine is used [12]. An ideal pertussis vaccine still eludes the healthcare and till that time effective control strategies need to be evaluated with the existing vaccines. Ironically, in spite of resurgence and outbreaks, no affected country is even thinking of reverting back to the available wP vaccines knowing fully well that such a retrograde step can lead to unprecedented disease burden due to non-acceptance of a reactogenic vaccine.

5. *Evasion of pre-existing immunity by the genomic changes in B. pertussis*: The microbe has a fairly stable genome but anecdotal reports of changed pretactin and fimbrial proteins have been reported [11,13-15]. The contribution of this change in the reported outbreaks is however not very convincingly demonstrated.

### THE INDIAN PERSPECTIVE

Whole cell DPT vaccines are and shall remain the backbone of immunization programs in India. A small proportion of urban population does get aP vaccines with wide regional variation, and are highly compliant with all the primary and booster doses because of their high socioeconomic and educational status. Further their augmentation of immunity keeps occurring in a background of suboptimal vaccination coverage and high circulation of the wild organism. At least in the foreseeable future, they do not seem to have a significant risk of the disease, and should not be denied the access to a low reactogenecity vaccine for the reason of outbreaks in developed countries with an entirely different epidemiology and vaccine policies. The priority is to increase the immunization coverage with whatever vaccine is preferred and affordable by the population. The existing vaccines must have stringent quality and regulatory control before they are licensed. The disease surveillance must continue to detect changes in epidemiology with the ongoing immunization programs. The efficacy of licensed vaccines if possible should be studied in different populations within the country to fine tune effective control strategies.

### THE WAY FORWARD

- The quest for an ideal pertussis vaccine must continue towards low reactogenecity, high immunogenicity and prolonged protection. There is no one upmanship between the wP and aP vaccines as both have withstood the test of time and have their own merits and demerits.
- The surrogate for protection should be identified and standardized for comparability of the new and available vaccines.
- Disease surveillance should be strengthened to detect changes in epidemiology and identify populations with fast waning of vaccine immunity, and the probable reasons for the same to redesign population specific vaccine schedules.
- High and sustained immunization should be insured with whatever vaccine being used, for both primary and booster doses.

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## COUNTERPOINT

The author has discussed several reasons for the resurgence of pertussis in developed countries and try their level best to negate acellular pertussis (aP) vaccines as a significant reason for the same. They try to downplay the poor effectiveness of aP vaccines as an important reason for the outbreaks, and in the process try to project them almost as effective as whole cell pertussis (wP) vaccines and the later only slightly better than the former. In the end, they try to defend the use of aP vaccine in clinical practice in India and show apprehension that their use may be abandoned in the light of emerging evidence against aP products from industrialized countries.

1. The author has either chosen not to mention recent references that have categorically shown poor effectiveness of aP vaccines *vis-à-vis* wP vaccines in head to head comparison [1-4] or only selectively used a particular reference without sharing key findings of the same [5,6]. For example, the paper by Sheridan SL, *et al*. [6] concludes: "In all scenarios, the reported rates of pertussis were significantly lower among children who had started the vaccination process with DTwP than among those who had started with DTaP" [6].

   There may be several reasons for the upsurge of pertussis in all these countries as discussed by the authors, but the recent reports have analyzed subset of population and concluded that those who had received wP vaccines in the past were more protected than those who received all aP vaccines. These trials have concluded that not only faster waning, but aP vaccines were found to be wanted even for priming [1-6]. Hence, aP vaccines underperformed on both the fronts, i.e. primary induction and durability of immune responses. Studies conducted in US and Australia after the recent outbreaks have now conclusively proved that the change from wP to aP vaccines contributed to the increase in pertussis cases.

2. The author did not mention that when wP and aP were compared head to head, at least five studies showed that DTwP vaccines have greater efficacy than DTaP vaccines [7]. Still, the author tries to defend aP vaccines as "soft target." The perception that both the vaccines are of equal efficacy is based on older data and concepts.

3. The only advantage where aP vaccines score over wP is "reactogenicity". There is no difference between aP and the wP vaccines for rare severe events. Post-2012 outbreaks of pertussis in US, UK, and Australia have shifted the focus back on effectiveness of the pertussis vaccines from the safety. The Advisory Committee on Immunization Practices (ACIP) and many US experts on pertussis have also discussed the option of going back to wP vaccines. But the problem with them and with the entire western world is that they cannot now revert to wP vaccines owing to "poor public acceptance" of these products. Fortunately, this is not a big issue as yet in India. There is no report of poor acceptance or widespread rejection of wP vaccines both from the public or private sector.

4. Coming to "the Indian perspective", the author has tried to justify the equal emphasis accorded to aP vaccines (versus wP vaccines) despite any evidence in favor of the former. India is essentially a wP vaccine using country and more than 95% of children are still vaccinated with wP vaccines. There is no data on the efficacy/effectiveness of aP vaccines in India and almost all the recommendations are based on the performance of these vaccines in industrialized countries, mainly USA. The aP vaccines are licensed in India based merely on immunogenicity data. In the absence of any known reliable and consistent 'correlate of protection' of either pertussis disease or vaccines, the immunogenicity data become redundant and cannot be relied as a sole proxy of protection. On the contrary, we have strong evidence of effectiveness, real life performance of wP vaccines from India where the widespread use of them have markedly reduced the

incidence of pertussis. The incidence of pertussis declined sharply after launch of Universal Immunization Program (UIP). We have achieved a good control of pertussis (high effectiveness, not merely the efficacy) with whatever type of wP was available in the country despite with a modest coverage of around 60-70%. On the other hand, the epidemiology of pertussis and performance of wP and aP vaccines in US clearly shows that early use of wP vaccines had almost eliminated pertussis which has now resurged after use of even the highest quality aP vaccines with a very high coverage (close to 100%) since mid-1990s.

5. In the end, the author has shown a fear that affluent section of society may be deprived of "a low reactogenicity vaccine". On the contrary, by not offering them a higher efficacy vaccine, they are indeed deprived a chance to prime their kids with a superior product since even a single dose of wP vaccine offer significant resistance to future susceptibility to wild pertusisis as proved by recent studies [3,6]. Further, not 100% of kids are going to experience untoward reactions with the first dose of wP vaccine.

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