ILiAD Biotechnologies, LLC

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Next generation pertussis vaccine could halt rise in outbreaks

Preclinical and early clinical data show that ILiAD Biotechnologies' live, attenuated vaccine BPZE1 may be superior to current vaccines and provide a definitive solution to the dramatic resurgence of pertussis. It may also be the first pertussis vaccine capable of fully protecting vulnerable infants younger than 6 months old.

ILiAD Biotechnologies (ILiAD) is developing a new vaccine for pertussis, the disease better known as whooping cough. Most people incorrectly assume that in industrialized nations, pertussis, like polio, is a childhood illness of the past. However, pertussis has been on the rise for decades, even among highly vaccinated populations. ILiAD collaborators Institut Pasteur de Lille (IPL) and the French National Institute of Health and Medical Research (INSERM) successfully completed a phase 1 clinical trial of the BPZE1 vaccine demonstrating safety in adults. The phase 1 trial and preclinical studies in neonates provide a preliminary indication that BPZE1 may protect young infants better than current vaccines. In addition, an initial indication for adults could help prevent spread of disease from adults to infants.

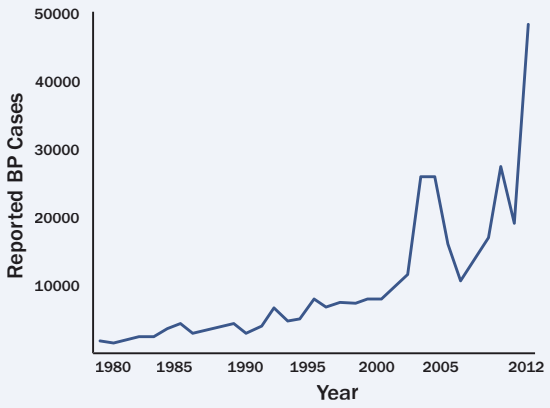

Figure 1: Reported pertussis incidence in the United States 1980–2012. The number of reported *Bordetella pertussis* (BP) cases reached a 50-year high in 2012, exposing a weakness in the current generation of vaccines. More than 75% of those infected in multiple US outbreaks were fully vaccinated. Data compiled from US Centers for Disease Control and Prevention.

Pertussis is a life-threatening disease caused by the highly contagious respiratory bacterium *Bordetella pertussis*. According to US Centers for Disease Control and Prevention, pertussis affects 30 to 50 million people globally, accounting for 300,000 deaths annually. From the introduction of the first vaccine in the 1940s until the 1970s, the number of cases of pertussis dramatically declined. But rates began to rise in the 1980s, and accelerated in the mid-1990s after the introduction of acellular pertussis (aP) vaccines. By 2012, the number of US cases reached a 50-year high. Although estimated global vaccination coverage is 84%, current vaccines have failed to control epidemics. In addition, current vaccines do not fully protect infants under age 6 months, since immunization requires multiple injections, usually at 2, 4 and 6 months.

ILiAD was formed in 2012 with a clear mission: global eradication of *B. pertussis*. ILiAD CEO and founder Keith Rubin suspected a pertussis problem almost a decade ago. Rubin, a physician who formerly specialized in the care of patients with HIV and AIDS, spent 6 years researching *B. pertussis* and concluded that the inability of existing pertussis vaccines to induce potent mucosal immunity had important implications. Although an aP-vaccinated individual might possess systemic immunity to *B. pertussis* and exhibit no symptoms of whooping cough, their nasopharynx could still harbor *B. pertussis*. Presence of the pathogen in the nasopharynx can lead to transmission to infants, who are particularly vulnerable. After a full year analyzing experimental therapeutics targeting pertussis, ILiAD identified BPZE1 as the most promising technology in development and subsequently licensed the vaccine from IPL and INSERM. The company continues to work in close collaboration with leading pertussis expert Camille Locht, research director at INSERM and head of the Center for Infection and Immunity at IPL.

Concerns over the US rise in pertussis cases led to a Food and Drug Administration (FDA) study using a new preclinical model for vaccine development. The study's findings, published in 2014[1], suggest that the United States pertussis problem is in part due to the failure of aP vaccines to prevent colonization of the nasal passages by *B. pertussis*, corroborating Rubin's hypothesis. ILiAD has since used the FDA preclinical model to study BPZE1 and found that after vaccination with BPZE1, subjects were protected against whooping cough and had 99.8% fewer *B. pertussis* bacteria colonizing the nasopharynx than subjects in the 2014 FDA study using aP vaccine.

ILiAD's vaccine is a single-dose, live, attenuated, intranasal vaccine engineered to eliminate or inactivate three key toxins. Preclinical mouse studies show that BPZE1 provides dose-dependent pertussis immunity with induction of antibodies and cells secreting interferon-γ, leading to potent mucosal and systematic immune responses. In addition to greatly reducing colonization in the study using the FDA preclinical model, BPZE1 demonstrated broader and longer-lasting immune responses than current aP vaccines in mice, and, to ILiAD's knowledge, BPZE1 is the only vaccine to demonstrate efficacy in a neonate preclinical model.

The results of the first-in-human phase 1 clinical trial were published in 2014[2] and established that BPZE1 is safe in healthy adults and, despite the relatively low dose and volume administered, induces immune responses targeting *B. pertussis*. ILiAD plans to build on these results by using a higher dosage and volume of BPZE1 in an upcoming clinical trial.

In addition to its efficacy with pertussis, researchers at IPL and INSERM serendipitously discovered that BPZE1 has therapeutic benefits for inflammatory diseases. ILiAD is particularly interested in developing BPZE1 as a treatment for asthma, a disease that affects more than 235 million people worldwide, with pharmaceutical costs projected to exceed $20 billion by 2019. Recent work by Locht and colleagues[3] demonstrated BPZE1's potent anti-inflammatory effects in an experimental allergic asthma model, with marked reductions in peribronchial inflammation and Th2 cytokines.

ILiAD is now optimizing manufacturing processes for BPZE1 in preparation for future trials and eventual commercialization. The current market for vaccines that include *B. pertussis* subcomponents is more than $3 billion per year, growing 7% annually, and BPZE1 is the leading next-generation pertussis vaccine. Rubin noted, "The performance of our vaccine thus far has been remarkable. BPZE1's ability to prevent colonizing infections may halt transmission and ultimately holds the potential to eradicate this devastating disease."

References

1. Warfel JM *et al*. *PNAS*. **111(2)**; 787-92 (2014).
2. Thorstensson R *et al. PLOS1*. **9**, e83449 (2014).
3. Li R *et al. Allergy*. **67**,1250–1258 (2012).

CONTACT DETAILS

Ken Solovay, Vice President of Development
ILiAD Biotechnologies, LLC
New York, NY
Tel: + 1 954 336 0777
Email: ken@iliadbio.com