Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination

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Abstract

A multidisciplinary workshop held from September 29 to October 1, 1989 at Airlie House, Warrenton, Virginia, considered the neurologic complications of whooping cough and pertussis vaccine.

Pertussis mortality in the U.S. in 2-3/1000 cases. Seizures occur in 1.9% of cases, and encephalopathy in 0.3%. Reviewing all data, it appears likely that a combination of one or more bacterial toxins, asphyxia, CO2 retention and loss of cerebral vascular autoregulation is responsible for neurologic symptoms. The timing of the encephalopathy suggests that it results from increased lysis of bacteria, and release of endotoxin. The encephalopathy is not confined to the paroxysmal phase.

In evaluating side-reactions to the vaccine, the following must be kept in mind:

1. Vaccines are not standardized between manufacturers.
2. For a given manufacturer, vaccines are not standard from one batch to the next.
3. Unless the vaccine is properly prepared and refrigerated, its potency and reactivity varies with shelf life.

In fact, the whole question of vaccine detoxification has never been systematically investigated.

Listed in order of increasing severity, observed adverse reactions include irritability, persistent, unusually high pitched crying, somnolence, seizures, a shock-like "hypotensive, hyporesponsive" state, and an encephalopathy. Since the neurologic picture is not specific for pertussis vaccination, its temporal relationship to the vaccination is the critical variable for determining causation.

Although the majority of seizures following pertussis vaccination are associated with fever, it was the consensus of the neurologists attending the workshop, that these do not represent febrile convulsions, but are non-benign convulsions.

The incidence of post-vaccine encephalopathy is difficult to ascertain. The most carefully conducted retrospective case-control study reported that the relative risk of a previously normal infant for the onset of an illness leading to encephalopathy with permanent subsequent disability was 4.2 times greater during the first 72 hours following DPT vaccination than in controls. From this study, the risk of permanent brain damage following DPT has been calculated as 1:310,000 doses.

It was the consensus of the workshop, and in particular the participating neurologists, that although the vaccine may possibly accelerate neurologic signs or symptoms in some children, and a small proportion of apparent complications may be coincidental, there was no inherent difficulty in assigning cause and effect to the vaccine and subsequent nuerologic residua.

It was also the consensus that there was no demonstrated association between DPT vaccination and SIDS, because sudden death after pertussis vaccination is too rare to be detectable in the context of the presently available series. Sudden death may occur in infants in the course of whooping cough, and following pertussis vaccination.

As was pointed out by several pediatric neurologists, the inherent problem in linking pertussis vaccination to infantile spasms is the extreme difficulty in determining the exact timing of their onset.

In implicating pertussis vaccination in the evolution of subsequent neurologic residua, a careful consideration of the mechanism for vaccine-induced brain damage plays an important supporting role. Pertussis toxin has been shown to alter cellular signaling. It also affects the catecholaminergic and GABergic systems in the brain. Although normally a protein of the size of PT (pertussis toxin) would not be able to cross the blood-brain barrier include brief hypertensive episodes such as might occur during a coughing paroxysm, hypoxia, and prolonged seizures, whether or not they are accompanied by hypoxia. In addition, a direct, endotoxin-mediated attack on the endothelial cells could create a local defect of the blood-brain barrier.

In summary, it was the consensus that there is sufficient experimental data to implicate both endotoxin and PT in adverse neurologic reactions to pertussis vaccine.

Key words

Pertussis vaccination -post vaccination encephalopathy - Pertussis

A multidisciplinary workshop held from September 29 to October 1, 1989, at Airlie House, Warrenton, Virginia, considered the neurologic complications of whooping cough and pertussis vaccine. The workshop enabled interaction between outstanding neuroscientists and some of the most prominent workers in the area of pertussis infection and vaccination.

Pertussis

As described by *James W. Bass* (Tripler Army Medical Center, Honolulu, Hawaii), whooping cough evolves in three phases (2). Patients are most contagious during the initial *catarrhal stage;* the *paroxysmal* stage which lasts from a few days to several weeks, is marked by the characteristic paroxysmal cough accompanied by vomiting and lymphocytosis. In newborns and young infants pertussis may however present with apnea and cyanotic spells, and a history of a cough may be elicited only if specifically sough for. The erythrocyte sedimentation rate remains normal in uncomplicated pertussis. The convalescent phase occurs when paroxysms subside but chronic cough persists.

Bordetella pertussis organisms are not invasive. They remain attached to the cilia of the respiratory epithelium.

Patients are usually afebrile: fever indicates a secondary bacterial infection. B. Pertussis produces 30 to 50 antigens and several toxins. The exotoxin, pertussis toxin (PT), has been most studied. Heat-stable toxins, including a lipopolysaccharide endotoxin, are also produced, as well as a tracheal cytotoxin factor (15,25).

Pertussis mortality in the U.S. is currently 2-3/1000 reported cases, although there is significant under reporting of cases. In Third World countries, mortality can be as high as 50%. Complications include bacterial pneumonia, seen in 16% of hospitalized children, sinusitis and otitis. Seizures are encountered in 1.9% of cases, and encephalopathy in 0.3%. Subdural or subarachnoid hemorrhage are rare complications.

When pertussis encephalopathy develops, it occurs during the first week of paroxysmal state in most cases. It is usually associated with fever, seizures, alterations of consciousness, and focal neurologic signs, notably acute visual loss in the presence of normal optic discs. It may be secondary to retinal changes induced by cough paroxysms. CT scans have been normal, but no MR imaging studies have been reported.

The cause of seizures in whooping cough is uncertain. In most instances, they are afebrile, and unrelated to the hypoxia which attends a coughing paroxysm. Hypoglycemia, which often attends whooping cough, is not known to be sufficiently severe to produce seizures, although CSF glucose has not been examined systematically. It is likely that seizures attending whooping cough represent a mild form of encephalopathy. There is no evidence that PT in isolation can induce encephalopathy. If this were the case, this complication should be seen during the catarrhal stage of the disease, when the highest concentration of B. Pertussis organisms occurs in the respiratory passages. Rather, the timing of the encephalopathy suggests that it results from increased lysis of bacteria, and release of endotoxin. It has, however, not been demonstrated that the endotoxin enters the blood stream. A heat-stable neurotoxin, distinct from PT, and related to endotoxin, has been demonstrated to induce convulsions in mice.

Pertussis encephalopathy is thought to be fatal in one-third of patients, leave neurologic residua, including learning disabilities, in one-third, the remainder of survivors being normal.

The neuropathology of whooping cough was reviewed by *William Bell* (University if Iowa, Iowa City, Iowa). Almost all published studies are old. The brain shows nonspecific alterations, notably swelling, anoxic-ischemic changes, venous congestion, and petechial hemorrhages (10). To an uncertain extent, these result from airway obstruction and metabolic derangements, in particular, the dehydration and metabolic alkalosis that result from vomiting which usually attends the coughing paroxysms. The role the various toxins of B. Pertussis play in the evolution of these neuropathologic alterations is unknown. Some encephalopathies develop in the absence of significant paroxysms.

Reviewing all data, it appears likely that a combination of one or more bacterial toxins, asphyxia, CO2 retention and loss of cerebral vascular autoregulation is responsible. In particular, hypoxia may result in a breakdown of the blood brain barrier, allowing the bacterial toxins to enter the central nervous system.

Pertussis Vaccine

The whole-cell vaccine and its preparation were reviewed by *John Cameron* (Institute Armand, Trappier, Laval, Quebec). All vaccines in current use in the U.S.A. and the U.K. are whole-cell vaccines. Production methods differ between manufacturers. Thus the US vaccine contains 1.7 times as many bacteria as vaccines recommended by the WHO. In essence, whole-cell vaccine is produced from several bacterial strains that differ in serologic composition. Various factors, notably the number of subcultures used and the medium on which bacteria are grown affect the concentration of the various bacterial antigens. Organisms are killed by heat, methiolate or formalin. There is therefore considerable variation from manufacturer to manufacturer with respect to toxicity, potency, and histamine content of the vaccine. In addition, the significance of the various antigens relative to vaccine effectiveness and toxicity is unknown.

Various in-process tests have been used. These include a test for the general safety of the vaccine, the mouse toxicity test. This nonspecific test is related in the number of organisms and the lipolysaccharide (LPS) content of the vaccine. An opacity test, a potency test, and determination of serologic components and stability are also employed. After its preparation, the pertussis vaccine is added to tetanus and diphtheria toxoids and is adsorbed on aluminum phosphate.

In evaluating side-reactions to the vaccine, the following must be kept in mind.

1. Vaccines are not standardized between manufacturers.
2. Even with the same manufacturer, vaccines are not standard from one batch to the next.
3. Unless it is properly prepared and refrigerated, the vaccine's potency and reactivity varies with shelf life.

It is therefore evident that at least some of the differences between various studies on the incidence of adverse reactions to vaccines reflect differences in the vaccines used.

Neurological vaccine injuries

The neurologic complications of pertussis vaccination were reviewed by *Edward Mortimer* (Case Western Reserve University, Cleveland, Ohio) and by *Jean Aicardi* (Hospital des Enfants Malades, Paris). In ascending order of severity, these are fever, irritability, persistent unusually high pitched crying, excessive somnolence, **seizures**, a shock-like "**hypotensive, hyporesponsive**" state, and **encephalopathy**. These complications have been described in numerous publications, commencing with those of *Madsen* (5, 7, 9, 20).

In *Aicardi's* personal series of 20 cases of seizures or encephalopathy, the onset was within 72 hours, and usually within 24 hours of pertussis vaccination. Seventy-five per cent of his cases developed within 12 hours of the vaccination and 80% within 24 hours, a pattern often reflected in the literature and not compatible with the notion of a chance association (22). Neurologic complications most often followed the first vaccination. There was frequently a change in consciousness, most characteristically coma of several day's duration, followed by an abrupt arrest in development. Seizures tended to assume the form of **convulsive status epilepticus** or of **severe myoclonic epilepsy**. This entity, which is usually seen unrelated to DPT vaccination, has its onset with uni- or bilateral clonic seizures in a setting of fever, which often is low grade. Initial attacks are followed by myoclonic seizures, atypical absence attacks. or complex partial seizures, and are accompanied by progressive mental deterioration. The EEG is initially normal in some 75% of cases, but tends to deteriorate. The CSF is usually normal.

Since this neurological picture is not specific to pertussis vaccination, its temporal relationship to vaccination is critically important for determining its cause. Inasmuch as subsequences are not necessarily consequences, several epidemiologic studies have been attempted in order to relate the incidence of apparent vaccine reactions to the background rate of infantile encephalopathy, and to ascertain whether pertussis vaccine renders prematurely overt the inevitable manifestations of a pre-existing disorder.

Analytical epidemiologic studies may be divided into prospective cohort studies, and retrospective case control studies.

The best designed prospective cohort study is that of *Cody* et al (7) which compared adverse reactions of DPT and DT vaccination. Persistent crying was common with DPT. Seizures followed 0.06% and the hypotensive-hyporesponsive state followed 0.06% of DPT vaccinations. As was subsequently noted in the workshop, these complication did not follow immunization with the Swedish acellular pertussis vaccine. Not surprisingly, the prospective incidence of seizures in this study is greater in retrospective studies such as those of *Ehrengut* (12) (1:2200), or *Strom* (14,29) (1:6500). Of the other prospective case-control studies (14,26) some indicate similar incidences, whereas others did not show an excess of seizures during the first 72 hours following vaccination (31).

Although the majority of seizures following pertussis vaccination are associated with fever, it was the consensus of the neurologists, that they could not be described as febrile convulsions,

because they are not necessarily benign. Follow-up studies of children in the *Cody* series who experienced seizures or the hypotensive/hyporesponsive state following DPT did not disclose any sequelae (1), but the sample size was far too small for conclusions to be drawn. The absence of permanent complications or seizures in their sample contrasts with a 10% incidence of permanent residua, but a lower incidence of seizures in retrospective studies such as those of *Ehrengut* or *Strom*. Clearly, seizures without sequelae tend to be forgotten.

Because vaccine-induced encephalopathy is so rare, a case-control study is appropriate. Diseased individuals are identified, case controls are selected, and the timing of exposure to the vaccine is asserted retrospectively.

The only retrospective case-control study is that conducted in the U.K. (23). This study reported that the relative risk of a previously normal infant for the onset of an illness leading to permanent encephalopathy was 4.2 times greater during the first 72 hours following DPT vaccination than in controls. From this study, the risk of permanent brain damage following DPT has been calculated as 1:310,000 doses, with the 95% confidence interval being 1:50,000 to 1:18,000,000.

Mortimer listed the following doubts about the NCES results (6)

1. A possible selective referral of DPT recipients.
2. Similar effect following DT administration.
3. An admittedly non-significant decreased risk for encephalopathy, 7 were said to have had other diseases.

In view of these reservations, Mortimer felt that it was not possible to prove an absolute negative, namely that there was not such an entity as post-pertussis vaccine encephalopathy, and even if this entity did exist, its incidence was too low to be measurable.

With respect tot he suggestion that pertussis vaccine might accelerate the clinical onset of a latent disease, *Kinsbourne* (Shriver Center, Waltham, Mass) pointed out that no mechanism exists which would do so without rendering such a disease more severe.

It was the consensus of the workshop, in particular of the participating neurologists, that regardless whether on rare occasions, the vaccine may accelerate the appearance of neurologic signs or symptoms of an underlying disease, and some apparent complications may be coincidental, there was no problem with assigning a cause and effect relationship between vaccination and subsequent permanent neurologic residua.

Pertussis vaccination and SIDS

The relation between pertussis vaccine and SIDS was examined *by Donald Peterson* (University of Washington, Seattle, WA). He defined SIDS as the sudden death of any infant, unexpected by history, in which a thorough postmortem examination fails to demonstrate an adequate cause of death. the diagnosis of SIDS is far from precise, and several entities, including infantile botulism, homicide, idiopathic infantile apnea, and malignant hyperthermia are responsible for a significant proportion of SIDS cases. The bulk of cases probably have some as yet undefined etiology. The incidence, 2/1000, has been relatively constant over the last twenty years. Sudden death occurs in whooping cough. In some instances, it accompanies a paroxysm, in others it results from apnea associated with a characteristic paroxysm.

No increased risk for SIDS during the first 24 hours following DPT immunization could be found in the Tennessee study (17) and in the retrospective study of *Hoffman* et al (18). To the contrary, the incidence of DPT vaccination was lower in SIDS infants than in control infants. This is apparently because children in chronic ill health, which is a risk factor for SIDS, often remain unvaccinated. In contrast, *Walker* and coworkers (30) found the SIDS morbidity rate

from 0 to 3 days following immunization to be 7.3 times that during the period beginning 30 days after immunization. Peterson pointed out that this study suffered from the deficiencies of retrospective cohort studies. Additionally, *Walker* failed to control for a shift in the time of the first DPT vaccination to a later age at which the incidence of SIDS is at its height.

David Lane (School of Statistics, Univ. of Minnesota, Minneapolis, MN) reviewed the problems inherent in attempts to examine the association of relatively common events, such as SIDS, and a superimposed rare event such as DPT vaccine encephalopathy. For statistically reliable validation of disproof of pertussis vaccine-induced SIDS, a population of five million children would have to be studied. Since such a project is manifestly unworkable, other strategies have to be used. He favored pooling data from several studies. Thus if each individual study showed a slight inclination to an excess risk, pooled data might disclose an effect which could not be demonstrated otherwise. *Kinsbourne* commented that this logic extends to pooling published case reports, which over more than five decades have documented encephalopathic reactions to pertussis vaccine, but rarely to other vaccines.

It was the consensus of the participants that an association between DPT vaccination and SIDS has not been demonstrated. When sudden death occurs in infants in the course of whooping cough and following pertussis vaccination it is preceded by encephalopathic symptoms and therefore does not meet the criteria of SIDS. If indeed sudden death occurred from anaphylactic shock, and if a small proportion (some 1%) of sudden deaths in infants were due to DPT vaccination, this association is too rare to be detectable from presently available data which lumps these infants together with those properly diagnosed as SIDS.

Martin Bellman (Child Development Center, London) reviewed the relationship between DPT vaccination and infantile spasms (4). The NCES study, in which he participated, found no positive evidence to link these two events. The relative risk of 2.46 for the onset of infantile spasms within one week of DPT immunization was not significant, and had to be compared with a relative risk of 2.0 in DT immunized infants. For both series there was an excess of cases during the first six days following vaccination followed by a non-significant deficit over the ensuing three weeks. This could reflect a tendency for parents to use immunization as a retrospective marker for the onset of infantile spasms. Studies by Melchior (21) and Fukuyama et al (16) have supported the thesis that the onset of infantile spasms is unrelated to DPT vaccines.

Kinsbourne pointed out that negative results attributable to lack of statistical power cannot be used to make negative inferences. In the Fukuyama study, two cases of infantile spasms out of 110 in which there was detailed information as to past vaccination history had the onset of seizures within two days of vaccination. In these two cases no injurious factors other than vaccination served as etiology. Inasmuch as the etiology for infantile spasms was known or suspected in all but 12 of the 110 cases, one might conclude that DPT vaccination is a likely, albeit unproven, cause for some 16% of cases of idiopathic (cryptogenic) infantile spasm. The incidence of chance occurrence within two days of vaccination was 2%. Whereas these numbers are too small to permit statistical analysis, they cannot be used to conclude that there is no relationship.

The *Melchior* study intended to examine the effect on the onset of infantile spasms of a change in the time of initiating DPT vaccine in Denmark from 5 months to 5 weeks. *Kinsbourne* pointed out that prior to the acceleration of the vaccination schedule, 12% of cases of infantile spasms had their onset before two months of age as compared with 23% after the change in schedule. These figures are also consistent with the supposition that a minority (11%) of infantile spasm cases is vaccine-induced.

Relative to these and several other studies including the recent one of *Shields* and coworkers (27) examining the linkage between infantile spasms and DPT vaccination, *Aicardi* and other pediatric neurologists attending the workshop, pointed out the extreme difficulty in

determining the exact timing of the onset of infantile spasms. Further to the issue of cause and effect, *Kinsbourne* remarked that with respect to the more usual, encephalopathic, consequences of pertussis vaccination, given that seizures, often prolonged are an undisputed acute consequence, it would be unprecedented if they never led to epilepsy, and that as a shock-like state is an equally undisputed adverse reaction, it would be surprising if it never led to brain damage or death. A continuum of severity is the rule in symptoms of neurological disease.

In implicating pertussis vaccination in the evolution of subsequent neurologic residua, evidence as to possible mechanisms for vaccine-induced brain damage plays an important supporting role.

Pathogenesis of vaccine injury

Peter Behan (Southern Central Hospital, Glasgow) incriminates several pathogenic mechanisms in post-pertussis vaccine encephalopathy. The major one develops within 24 hours of immunization, but another mechanism remains active up to one week following immunization. He stressed that before two years of age the immature brain cannot react to autoimmune challenge. As a consequence, neuropathological examination of infants succumbing to pertussis vaccination cannot be expected to confirm this mechanism of brain damage.

Behan reported on 49 autopsied cases of acute hemorrhagic leukoencephalopathy (3). Whooping cough was responsible for four of these, and DPT vaccine for one. The pathological picture was compatible with an endotoxin-induced generalized *Schwartzman* reaction, which activates complement and produces endothelial damage. *Bell* pointed out that endothelial damage had not been observed in brains of other patients succumbing to whooping cough. Most of these were infants, however, and these changes would not be expected. *Behan* found that in the majority of cases the LPS component is responsible for endothelial cell damage. This is supported by several experimental studies cited by *Kinsbourne*. The endothelial cells of the blood-brain barrier may be particularly susceptible to complement mediated antigenic attack.

William Olendorf (Brentwood V.A. Hospital) found that brain endothelial cells have a higher density of mitochondria than other types of endothelial cells, and that they are antigenically unique.

Although the *Schwartzman* reaction is responsible for the majority of vaccine-related neurological complications, particularly those that evolve within 24 hours of vaccination, others may be caused by anaphylactic reaction. In yet others, a concurrent benign infection may act in conjunction with the vaccine to produce the *Schwartzman* reaction.

The effects of pertussis toxin on cellular signaling were reviewed by *Toshiaki Katada* (Tokyo Institute of Technology, Yokohama). His group has shown that the G proteins are the target of pertussis toxin (19). G proteins are guanine nucleotide-binding cells surface receptors for a number of hormones and neurotransmitters. They act by controlling adenyl cyclase activity. Pertussis toxin causes several of the G proteins to be ADP-ribosylated (11). This reduces their affinity for GTP, and reduces the release of GDP from GTP. although PT has no direct effect on GTPase activity, it prevents activation of GTPase. Since PT is covalently bound, binding is irreversible.

Pertussis toxin-induced ADP ribosylation impairs the ability of a cell to react with receptors. Thus PT abolishes the opiate-induce hyperpolarization of locus ceruleus neurons and reduces or abolishes the late inhibitory post-synaptic potential of hippocampal neurons. It also reverses adenosine inhibition of neuronal glutamate release.

Solomon Moshe (Albert Einstein School of Medicine, Bronx, NY) reviewed the epileptogenesis in the immature brain (24). The immature brain is more susceptible to seizures than the adult brain. There are many factors that can influence seizure susceptibility as a function of age, including differences in catecholamine content, and response to GABAergic drugs. Pertussis toxin can affect both catecholaminergic and GABAergic systems, but the interactions are complex and depend on the site to which pertussis toxin is applied. Both faciliatory and inhibitory effects have been reported. To date there are no experimental studies on the epileptogenicity of pertussis toxin in the immature brain.

Oldendorf reviewed the physiology of the blood-brain barrier. Being a protein, PT would not be expected to cross the blood-brain barrier under physiological conditions even in the immature and fetal brain. Factors known to disrupt the blood-brain barrier include brief hypertensive episodes such as might occur in a coughing paroxysm, hypoxia, osmotic agents such as mannitol, and prolonged seizures, with or without hypoxia (8). In particular, a direct endotoxin-mediated attack on the endothelial cells could create a local defect of the blood-brain barriers (13).

In summary, it was the consensus that there is sufficient experimental data to implicate both endotoxin and PT in adverse reactions to pertussis vaccine.

Alternative Vaccines

In view of the severity of adverse reactions to the currently used vaccines, considerable effort has recently been directed to the development of alternative vaccines. The Swedish trial of acellular vaccines was reviewed by *Jann Storsaeter* (Karolinska Institute, Stockholm) (28).

Two vaccines, one containing pertussis toxin (JNIH #7), the other pertussis toxin and filamentous hemagglutinin (JNIH #6), were compared with a placebo which contained the carrier solution of the vaccines (formalin, thiomersal and aluminum phosphate). JNIH#6 has been used in Japan since 1981 to immunize children over two years of age. Vaccine and placebos were administered subcutaneously. (According to *Cameron* this route of administration would be expected to induce a higher incidence of local reactions than intramuscular injection.) Except for persistent crying there were no significant side reactions. No seizures or hypotensive/hyporesponsive states were seen in 2847 infants. The vaccines were considered to be 74% and 86% efficacious, respectively. Vaccine JNIH#6 protected better against mild cases of pertussis, both vaccines were equally effective against severe cases. However, the development of invasive bacterial disease over the course of subsequent months in 1.5/1000 infants vaccinated with JNIH#6 resulted in discontinuation of the vaccine trials, although no relationship between these miscellaneous infections and the vaccine has been suggested (28). *Reno Rappuioli* (SCLAVO, Siena, Italy) pointed out that the acellular vaccines also include active toxins, and that formalin does not fully denature PT. According to Cameron, vaccine detoxification has never been fully investigated.

Rappuioli reviewed the preparation of a new genetically recombinant vaccine.

Of the several candidate molecules for the vaccine, pertussis toxin (PT) was selected. Adenylate cyclase, although important in virulence, was difficult to purify. The 69 Kdalton protein was a good antigen, but it too has not been purified in sufficient quantities. Although it was protective against the aerosol challenge, immunization with 69 KD protein did not protect against intracerebral challenge.

PT consists of five subunits, arranged into two domains. Domain A, consisting of the S1 subunit, is the active molecule in terms of toxicity and antigenicity, whereas domain B is necessary for binding of the protein to the cell surface. The S1 subunit, being devoid of lysine, is not readily detoxified with formalin, and either domain alone provides no protection. The gene for pertussis toxin has now been cloned, and a change in the amino acid sequence of S1

results in loss of conformation structure of the subunit and as a consequence, a loss of ADP ribosylation of the G proteins. As a result of this modification, toxicity was reduced by 106 but antigenicity was preserved.

This new recombinant vaccine is to enter Phase 1 clinical trials in the near future. Not only should this vaccine give rise to fewer toxic reactions, but anaphylactic reactions should be fewer as well, since the unmodified potentiates anaphylaxis. Workshop participants foresaw that once the recombinant vaccine receives widespread use, its reduced toxicity will result in increased acceptance by the public of vaccinations against pertussis, and with it a resumed decline in the incidence of the disease.

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