Scrutiny of Acts and Regulations Committee
Parliament House, Spring Street
EAST MELBOURNE, VIC 3002

27 September 2015

To The SARC Committee,

I am writing this submission to object to the proposed Public Health and Wellbeing Amendment (No Jab No Play) Bill 2015. Most specifically, I object to the removal of the Conscientious Objection exemption based on personal or philosophical beliefs.

As the mother of two young children (aged four and twenty months), this proposed legislation will profoundly impact the educational outcomes of my children as it will prevent them from being enrolled in four year old kindergarten. Early childhood education is a vital part of the formative years for every individual. From an economic perspective, it also limits the potential of our family to earn an income by removing access to child care.

I firmly believe that when there is potential for risk of harm, then there needs to be an informed choice for every individual, without fear of discrimination or the removal of access to fundamental services like education. Before making the decision not to vaccinate my children, I carefully considered all of the available documentation regarding vaccination, including multiple readings of the Immunisation Handbook of Australia, did extensive reading on Government websites in Australia and Internationally (e.g. the Centre for Disease Control in the Unites States), undertook extensive research of peer reviewed journal articles about different facets of vaccination, was counselled by my General Practitioner and sought the advice of other Health Practitioners.

My main concerns about vaccinations are:

- the number of vaccines in the schedule has almost tripled in my lifetime (at present, 41 vaccines given in 15 doses by the age of 4; in 1982 it was 16 vaccines given in 8 doses)
- multiple vaccines are given in each dose
- the long list of ingredients in each vaccine
- the one-size fits all approach to the scheduling of vaccines and the dosages that are injected
- the documented risks for every vaccine on the schedule
- the potential for irreparable harm if the vaccine is administered in the correct dosage and manner intended
- the lack of data available for things like the impact on fertility or overdose (see the Infantrix hexa datasheet for clarification, attached)
- there is no established way of testing whether a child will have an adverse response to a vaccine (the vaccine itself is the test)
- the fact we have do not have a vaccine compensation scheme in Australia for individuals who are harmed by vaccinations (as exists in 19 countries including the US and New Zealand; $3.2billion has been paid out to vaccine damaged individuals in the United States alone)
- The only member of my family who has had whooping cough is fully vaccinated.

According www.humanrightscommission.vic.gov.au/index.php/discrimination (accessed 27/9/15), "discrimination is treating, or proposing to treat, someone unfavourably because of a personal characteristic protected by the law" and discrimination may be direct or indirect. In Victoria it is against the law to discriminate against you because of a disability you have, or that people think you might have.

- "Disability includes the presence of organisms (such as HIV or Hepatitis C) that may cause disease or disability, malformation or disfigurement of the body".
- In the instance of a perfectly healthy, un-vaccinated child, this proposed legislation directly discriminates against the child, based on the potential that at some point in the future, they could have the presence of organisms that may cause disease.
- In Victoria, a child who has Hepatitis B is allowed to attend kindergarten and child care because legally, they are not allowed to be discriminated on the basis of their disability, regardless of the risks they pose to the other children. In direct contrast, this legislation will directly discriminate against a healthy child who is disease free, but has not been vaccinated against Hepatitis B.
- How is it that a child who actually has Hepatitis B is allowed to attend kindergarten and child care and cannot be discriminated against, yet, a perfectly healthy child who is free from disease, but not vaccinated, will not be allowed to attend kindergarten or child care and will be allowed to be discriminated against? It simply does not make sense.

According to www.humanrightscommission.vic.gov.au/index.php/discrimination (accessed 27/9/15), indirect discrimination includes "discriminatory behaviours and actions that affect a person or group with certain personal characteristics can become entrenched in an organisation or community. These behaviours often become part of organisation's culture and are reinforced by policies or procedures."

- Vaccination rates are currently 92% in Australia. We have a high rate of compliance for full vaccination; currently amongst the highest rates experienced historically. Conscientious objectors are an extremely small minority group; they only represent 1.61% of the Australian population. Even if every conscientious objector was to vaccinate, we would still fall short of the 95% coverage that is the current goal.
- In the mainstream media, unvaccinated individuals are constantly blamed for the spread of disease, especially whooping cough, despite the research about the different strains that are circulating in Australia, the problems associated with 'waning immunity' and the efficacy of the vaccine. The result is systemic discrimination against a small minority group of conscientious objectors. The proposed legislation is punitive in nature, and has been fueled by a very biased mainstream media.

The Governmental and mainstream media rhetoric is always that vaccinations save lives and are supported by extensive scientific research. In the case of whooping cough (*Bordetella Pertussis*, or B. pertussis), please consider the following points:

- According to Octavia et al. (2012), the data collected from studying the 2008-2010 pertussis epidemic suggest "increasing selection among the B. pertussis population in Australia in favor of strains carrying antigens that differ from those represented in ACVs" (Acellular Vaccines).
- Specifically, there was an increase from 31% (2000-2007) to 86% (2008-2010) of strains carrying antigens which differ from those represented in the ACV. (Journal article is attached.)

- Thus, of the strains circulating in Australia, it may be deduced that only 14% were covered by the vaccine and the rest of the strains were not covered by the vaccine. Vaccinated individuals are contracting and spreading whooping cough because whooping cough is ever changing and evolving under vaccine pressure.
- These findings are similar to what is being experienced in the United States. According to www.cdc.gov/maso/facm/pdfs/BSCOID/2013121112_BSCOID_Minutes.pdf (accessed 27/9/15), "a recent study suggests another explanation for decreased vaccine effectiveness… findings indicated that 85% of the isolates were PRN-deficient and vaccinated patients had significantly higher odds than unvaccinated patients of being infected with PRN-deficient strains. ***Moreover, when patients with up-to-date DTaP vaccinations were compared to unvaccinated patients, the odds of being infected with PRN-deficient strains increased, suggesting that PRN-bacteria may have a selective advantage in infecting DTaP-vaccinated persons.***" (p.6). The last point indicates that a vaccinated individual may be more likely to be infected with whooping cough than an unvaccinated individual.
- Collectively, these findings highlight how unjust these laws are. It is completely unreasonable that a healthy child (who does not have the presence of any organisms that cause disease such as whooping cough), will be systemically discriminated against and prevented from receiving an early childhood education on the basis that they are not fully vaccinated, when fully vaccinated individuals have the potential to contract and spread diseases like pertussis, and according to some research, are more likely to be infected when compared to unvaccinated patients.

With regards to the Victorian Charter of Human Rights and Responsibilities, I believe that the following sections will be breached:

Section 8: Right to recognition and equality before the law.

Please refer to my arguments regarding discrimination. Every person has the right to enjoy their human rights without discrimination, even if they have personal or philosophical beliefs that are contrary to the Government recommendations.

Section 10: Protection from torture and cruel, inhumane or degrading treatment.

Leveraging health against education (in this case, either vaccinate your child (health) or they will not be allowed to go to kindergarten (education)), is cruel and degrading treatment of partially vaccinating or non-vaccinating families. The proposed legislation purposefully designed to force compliance without passing a law which explicitly mandates vaccination. Furthermore, Section 10 protects individuals from medical treatment without full, free and informed consent.

According to the Australian Immunisation Handbook;

"Valid consent can be defined as the voluntary agreement by an individual to a proposed procedure, given after sufficient, appropriate and reliable information about the procedure, including the potential risks and benefits, has been conveyed to that individual.

For consent to be legally valid, the following elements must be present:

1. It must be given by a person with legal capacity, and of sufficient intellectual capacity to understand the implications of being vaccinated.

2. **It must be given voluntarily in the absence of undue pressure, coercion or manipulation.**
3. It must cover the specific procedure that is to be performed.
4. It can only be given after the potential risks and benefits of the relevant vaccine, risks of not having it and any alternative options have been explained to the individual."

(http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part2~handbook10-2-1#2-1-3, accessed 23/08/15)

Section 13: Right to privacy and reputation

If punitive laws about vaccination are passed, I am concerned that my children will be discriminated against by teachers, enrolment officers and other people who are in positions of power in educational institutions and that the reputation of my family may be compromised, whenever private information about vaccination history is disclosed.

Section 17: Protection of families and children

The role of a parent is to love and protect their children with their best interests in mind. The only exemption that is included in the proposed legislation is a medical exemption, and that is only obtained if a child has already had an adverse reaction to a vaccine. Under this legislation, a child has to be harmed by a vaccination in order to be exempt from having future vaccinations. Plus there is no avenue for recourse or compensation in Australia. This nullifies a parent's right to make decisions about what is best for their children, based on the information they have at the time.

Vaccine damage cannot be undone and each individual should have the right to choose whether to provide valid consent for a vaccination that has documented risks, without fear of being stripped of education, social security payments or anything else deemed fair game in the future. The rights of an individual to choose what happens to their own body should not be leveraged when there are other non-punitive strategies which can be used to increase an already high vaccination coverage. These laws have the potential to set a frightening precedent which will profoundly undermine individual autonomy and an individual's right to choose what happens to their body.

Thank you for taking the time to read my submission.

Regards,

Anonymous

(Government employee)

Encl.

Infantrix hexa datasheet (New Zealand version)

Octavia, S. et al (2012) Newly Emerging Clones of Bordetella pertussis Carrying prn2 and ptxP3 Alleles Implicated in Australian Pertussis Epidemic in 2008–2010, JID.

INFANRIX® hexa **New Zealand Datasheet**

NAME OF THE MEDICINAL PRODUCT

INFANRIX hexa
Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder and suspension for injection.

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU)
Tetanus toxoid[1]	not less than 40 International Units (IU)
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms 20 - 40 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed.

The Hib component is presented as a white powder.

Excipients

Lactose, sodium chloride (NaCl) and water (H_2O) for injections. Medium 199 (as stabiliser containing amino acids, mineral salts, vitamins and other substances) , potassium chloride (KCl), disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate and polymyxin B sulphate are present as residuals from the manufacturing process.

PHARMACEUTICAL FORM

Powder and suspension for injection.

CLINICAL PARTICULARS

Therapeutic indications

INFANRIX hexa is indicated for primary immunisation against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b in infants from the age of 6 weeks and may be given to infants who received a first dose of hepatitis B vaccine at birth.

Posology and method of administration

Posology

The primary vaccination schedule (such as 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months; 3, 5 and 11 or 12 months; 6, 10, 14 weeks) consists of three doses of 0.5 ml. An interval of at least 1 month should be respected between doses.

If it is intended to administer INFANRIX hexa according to the EPI schedule (Expanded Program on Immunisation; 6, 10, 14 weeks of age), then the vaccinee must receive a dose of hepatitis B vaccine at birth.

Available data indicate that the vaccine can be given as a fourth dose. However, the data are limited and therefore no recommendation is made for using this combination vaccine as a fourth (i.e. booster) dose during the second year of life.

Infants should receive booster vaccination with other licensed vaccines according to official local recommendations, where available.

Method of administration

INFANRIX hexa is for deep intramuscular injection.

Contra-indications

INFANRIX hexa should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients or residuals (see Excipients) or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

INFANRIX hexa is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Special warnings and special precautions for use

As with other vaccines, administration of INFANRIX hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered :

- Temperature of $\geq$ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting $\geq$ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

INFANRIX hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

INFANRIX hexa SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVASCULARLY OR INTRADERMALLY.

INFANRIX hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

INFANRIX hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis,* hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see section Pharmacodynamic properties).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of INFANRIX hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered to be a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that INFANRIX hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

High incidence of fever (> 39.5°C) was reported in infants receiving INFANRIX hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of INFANRIX hexa and Prevenar 13 (see Adverse Reactions).

Antipyretic treatment should be initiated according to local treatment guidelines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interaction with other medicinal products and other forms of interaction

There are insufficient data with regard to the efficacy and safety of simultaneous administration of INFANRIX hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of INFANRIX hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a three dose primary vaccination.

However, high incidence of fever (>39.5°C) was reported in infants receiving INFANRIX hexa and Prevenar compared to infants receiving the hexavalent vaccine alone (see Special warnings and special precautions for use).

INFANRIX *hexa* should not be mixed in the same syringe with any other vaccine.

As with other vaccines it may be expected that in patients receiving immunosuppressive therapy or patients with immunodeficiency, an adequate response may not be achieved.

Fertility

No data available.

Pregnancy and lactation

INFANRIX hexa is not intended for use in adults. Information on the safety of the vaccine when used during pregnancy or lactation is not available.

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

- Clinical trials:

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with INFANRIX hexa with respect to the primary course.

Frequencies per dose are defined as follows:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000to < 1/100
Rare: ≥ 1/10000to < 1/1000
Very rare: < 1/10000

Infections and infestations
Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders
Very common: appetite lost

Psychiatric disorders
Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders
Uncommon: somnolence
Very rare: convulsions (with or without fever)***

Respiratory, thoracic and mediastinal disorders
Uncommon: cough**
Rare: bronchitis

Gastrointestinal disorders
Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders
Common: pruritus**
Rare: rash
Very rare: dermatitis, urticaria**

General disorders and administration site conditions
Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)*, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint*

- Post-Marketing Data**:**

Blood and lymphatic system disorders:
Lymphadenopathy, thrombocytopenia

Immune system disorders:
Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders:
Collapse or shock-like state (hypotonic-hyporesponsive episode)***

Respiratory, thoracic and mediastinal disorders:
Apnoea*[*] *[see section "Special Warnings and Special Precautions for use" for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders
Angioneurotic oedema[**]

General disorders and administration site conditions:
Extensive swelling reactions, swelling of the entire injected limb*, vesicles at the injection site

* Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

**observed with other GSK DTPa-containing vaccines

*** Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of INFANRIX hexa with Prevenar 13 to those which reported use of INFANRIX hexa alone.

Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdose

Insufficient data are available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code JO7CA

Result obtained in the clinical studies for each of the components are summarised below :

- DTPa component:
  One month after the 3-dose primary vaccination course, 98.5 to 100% of infants vaccinated with INFANRIX hexa had antibody titers of ≥ 0.1 IU/ml for both tetanus and diphtheria. The overall response rates for each of the three individual pertussis antigens (PT, FHA, pertactin) were 97.2-99.3%, 95.2-100% and 95.9-99.3%, respectively.

- Hepatitis B component:
  When the EPI schedule is excluded, then after the primary vaccination course with INFANRIX hexa, 98.5 to 100% of infants developed protective antibody titers of ≥ 10 mIU/ml. In order to ensure an adequate response to the hepatitis B component children who will be vaccinated in the EPI schedule must receive a dose of hepatitis B vaccine at birth. In a study in which the EPI schedule was applied after a dose of hepatitis B vaccine at birth, one month after the third dose, a seroprotection rate of 98.5% was obtained.

- IPV component:
  One month after the primary vaccination, the seroprotection rates for each of the three serotypes (type 1, 2 and 3) was 99.2 to 100%, 94.5 to 99.0% and 98.8 to 100% respectively.

- Hib component:

  One month after the three-dose primary vaccination course 96.0 to 100% of infants vaccinated with INFANRIX hexa had antibody titers of ≥ 0.15 µg/ml and 61.9 to 84.0% of infants had titers of ≥ 1.0 µg/ml.

  The effectiveness of the Hib component of INFANRIX hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a 7 year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was INFANRIX hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

The protective efficacy of Infanrix DTPa against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts inhouseholds where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%, which was not statistically different from the DTPw vaccine.

- a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%.

  In a follow-up of the same cohort, the efficacy for GlaxoSmithKline's Infanrix DTPa vaccine was found to be 84% up to 4 years of age.

Infanrix DTPa is an integral part of the INFANRIX hexa combination vaccine.

Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL PARTICULARS

Incompatibilities

INFANRIX hexa should not be mixed with other vaccines in the same syringe.

Shelf-life

The expiry date of the vaccine is indicated on the label and packaging. The date for last use corresponds to the last day of the month mentioned.

The shelf-life is 36 months.

Special precautions for storage

INFANRIX hexa should be stored at +2°C to +8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Nature and contents of container

The DTPa-HBV-IPV component is presented as a turbid white suspension in a syringe. Upon storage, a white deposit and clear supernatant can be observed.

The lyophilised Hib vaccine is presented as a white pellet in a glass vial.

The vials and syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and syringe with or without needles* in packs of one* or ten.

*not currently marketed

Instructions for use and handling

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib pellet should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

INFANRIX hexa must be reconstituted by adding the entire content of the pre-filled syringe containing DTPa-HBV-IPV to the vial containing the Hib pellet. After the addition of the DTPa-HBV-IPV vaccine to the pellet, the mixture should be well shaken until the pellet is completely dissolved.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 $\pm$ 3 °C) for at least 5 minutes before connecting the pre-filled syringe and reconstituting the vaccine.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C).

Withdraw the entire contents of the vial.

MEDICINE CLASSIFICATION

Prescription medicine

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BRIEF REPORT

Newly Emerging Clones of *Bordetella pertussis* Carrying *prn2* and *ptxP3* Alleles Implicated in Australian Pertussis Epidemic in 2008–2010

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Australia is experiencing a prolonged epidemic of pertussis that began in 2008. A total of 194 *Bordetella pertussis* isolates collected from 2008 through 2010 were typed by single-nucleotide polymorphism (SNP) analysis, by multilocus variable number tandem repeats analysis, and by *fim3*, *prn*, and *ptxP* sequence analyses. Strains with 2 closely related SNP profiles carrying *prn2* and *ptxP3* from the recently emerged SNP cluster I predominated. The data suggest increasing selection among the *B. pertussis* population in Australia in favor of strains carrying *prn2* and *ptxP3* under the pressure of acellular vaccine–induced immunity.

Pertussis has reemerged as a significant public health threat in populations with historically high vaccine uptake. The increasing disease rates have been reported in many countries [1–4], including Australia, in recent years. A particularly severe epidemic began in 2008, and at its peak, in 2009, it caused up to 35 000 cases, with an incidence of 156 cases per 100 000 population. In Australia, pertussis vaccine coverage is relatively high, averaging 92% for children aged <12 months and up to 95% for children aged 24 months [5]. However, in 2008, only 80.7% had received the booster dose scheduled for 5 years of age [5]. During the current epidemic, children aged 5–9 years were most severely affected, even though vaccine coverage has not changed in this age group, at least over the past 8 years [6]. Therefore, other factors in addition to waning vaccine-induced immunity must have contributed to this prolonged epidemic.

Pertussis vaccination in Australia was first implemented using a whole cell vaccine (WCV) during the 1950s, and use of the WCV continued until 1999. Acellular vaccine (ACV) was phased in beginning in 1997, and only ACV has been used since 2000. One ACV contains 3 components: pertussis toxin (Ptx), pertactin (Prn), and filamentous hemagglutinin (Fha); another ACV contains 5 components: Ptx, Prn, Fha, and the fimbrial antigens Fim2 and Fim3. The ACV used predominantly in Australia is the 3-component vaccine [7].

Previously, we characterized 208 Australian *Bordetella pertussis* isolates collected since the 1970s, using 3 molecular typing methods: multilocus variable number of tandem repeats analysis (MLVA) [7], typing of genes encoding antigens used in ACVs (*prn*, *ptxA*, *fim2*, *fim3*, and *fhaB*), and single-nucleotide polymorphism (SNP) typing [8]. We classified SNP types into several SNP clusters and documented an increase in prevalence of clusters I and IV and a decrease in cluster II in Australia after the introduction of ACV. Cluster I contains isolates with MLVA type (MT) 27 and antigenic profile 3 (AP3; *prn2*, *ptxA1*, *fim2-1*, *fim3A*, and *fhaB1*) or AP8 (*prn2*, *ptxA1*, *fim2*-1, *fim3B*, and *fhaB1*); cluster IV consists of isolates with MT70 and AP7 (*prn1*, *ptxA1*, *fim2-2*, *fim3A*, and *fhaB1*). Cluster II was associated with MT29 and AP4 (*prn3*, *ptxA1*, *fim2-1*, *fim3A*, and *fhaB1*). Australian isolates uniformly contained alleles *ptxA1* and *fhaB1*. In this study, we investigated strains of *Bordetella pertussis* recovered during 2008–2010 that are associated with the ongoing Australian epidemic.

METHODS

We collected 194 clinical *B. pertussis* isolates from 2008 through 2010 from 4 states across mainland Australia, including 77 isolates from New South Wales (NSW), 47 from South Australia (SA), 30 from Victoria (VIC), and 40 from Western Australia (WA). Isolates were obtained from patients living in the capital city of each state, where the majority of the states' residents are located. All available isolates were genotyped. The relatively small number available for

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typing reflects the fact that polymerase chain reaction (PCR) and serology are the preferred diagnostic methods for pertussis, with culture infrequently requested. The total number of cases in 2008–2010 was highest in NSW (29 311 notified cases), followed by SA (14 238 cases), VIC (12 647 cases), and WA (2693 cases). Therefore, the ratio of the number of isolates selected to the total number of cases was similar (2.4–3.3 isolates per 1000) for all states except WA (14.9 isolates per 1000 cases).

Bacterial isolates were inoculated on charcoal agar (Oxoid) supplemented with 10% horse blood and were cultured at 35°C for 3–5 days. DNA was then extracted and used for typing. The isolates were typed by a hairpin real-time PCR–based SNP typing assay [8], by MLVA of 8 variable number tandem repeat (VNTR) loci [7], and by allele typing of antigen genes *prn* and *fim3*, using a real-time PCR–based assay [9]. Isolates were assigned to clusters and SNP profiles (SPs) according to the protocol of Octavia et al [8]. The Simpson diversity index (D) for each typing method was calculated using an in-house program (MLEECOMP; available on request).

RESULTS

The set of 194 isolates was classified into 11 SPs; the geographic distribution of SPs in different Australian states is shown in Figure 1. Three SPs were from cluster I (13, 14, and 16) and included the majority (86%) of isolates; SP13 (n = 96) was the most common, followed by SP14 (n = 47) and SP16 (n = 24; Figure 2*A*). Only 2 isolates belonged to cluster II (SP17 and SP37), and the remaining 25 were unclustered (SP1, SP6, SP7, SP9, SP11, and SP18). The frequencies for both SP13 and SP14 were not significantly different across states, and there was no predominance in the distribution of these SPs (Figure 1). Although SP16 was not observed in SA, the overall frequency of SP16 was low, and the absence of SP16 in SA may be due to the small sample size.

MLVA typing resolved the isolates into 27 MTs, of which 9 have been previously observed in our collection of diverse *B. pertussis* isolates and 18 have not (Figure 2*B*). Of the latter, 7 were novel; that is, they had not been recorded in the publicly available international MLVA database (available at: http://www.mlva.net), which contains data for 5 of the 8 VNTR loci (VNTR1, VNTR3, VNTR4, VNTR5, and VNTR6) used in this study. The other 11 were subtypes of the previously reported MTs. The majority of isolates belonged to MT27 (46.3%) or MT214 (13.4%; Figure 2*B*). The range of different MTs was recorded within the predominant SPs (ie, SP13, SP14, and SP16). For example, 4, 11, 6, and 8 MTs were detected within SP13 isolates collected from patients in NSW, SA, VIC, and WA, respectively. For SP14, NSW and WA had 4 MTs each, while SA and VIC had 5 MTs each. NSW, the largest state in Australia, demonstrated the largest variations in SP16, with 9 MTs; VIC and WA had only 2 MTs each.

We typed only 2 of the 5 ACV antigen genes *fim3* and *prn* because we previously found that only these 2 antigen genes varied among recent Australian isolates [8]. The majority (141 [73%]) of the 194 isolates had the *fim3A* allele; the remaining 53 had the *fim3B* allele. For *prn*, 167 isolates (86%) carried the *prn2* allele, 20 had *prn1*, 4 had *prn3*, and 1 had *prn7*; *prn* from 2 isolates (L1301 and L1304) was not typeable. We also typed the *ptxP* promoter, which has 18 known alleles, one of which (*ptxP3*) has been associated with increased production of pertussis toxin [10]. A hairpin real-time PCR assay was designed to detect a SNP (G → A) located –65 bp of the *ptxP* region, which is unique to *ptxP3*. Our SNP typing determined the presence or absence of the *ptxP3* allele (non-*ptxP3* alleles include *ptxP1-ptxP2* and *ptxP4-ptxP19*). We found that 86% of isolates carried *ptxP3,* almost all of which also carried *prn2* (Figure 2*C*).

The markers analyzed in this study—SNPs, MLVA, *fim3*, *prn*, and *ptxP*—were combined to form a unique polyphasic genotype for each isolate to increase the resolution of subtyping. Overall, the 194 isolates were classified into 46 genotypes. The 77 NSW, 47 SA, 30 VIC, and 40 WA isolates were differentiated into 22, 15, 13, and 19 genotypes, respectively. Overall, the most common genotype (in 22% of isolates) was SP13, MT27, *fim3A*, *prn2*, and *ptxP3,* which represented 29% of isolates from NSW and 30% from VIC. In SA, 34% of isolates were genotype SP14, MT27, *fim3A*, *prn2*, and *ptxP3.* In WA, 33% of isolates were genotype SP13, MT214, *fim3A*, *prn2*, and *ptxP3.* VIC isolates were the most diverse (D = 0.887), followed by NSW (D = 0.878), WA (D = 0.869), and SA (D = 0.848). The distribution of genotypes was similar among the isolates from the eastern states of NSW and VIC and differed most from SA isolates.

DISCUSSION

B. pertussis isolates collected from 4 Australian states during an ongoing pertussis epidemic that began in 2008 were classified using SNPs, MLVA, *fim3*, *prn*, and *ptxP* typing. SNP cluster I strains, primarily SP13 and SP14, accounted for 86% of isolates (Figure 2*A*). This is a significant increase from our previous study of isolates collected between 2000 and 2007, in which SNP cluster I represented only 31% of isolates. This suggests increasing selection among the *B. pertussis* population in Australia in favor of strains carrying antigens that differ from those represented in ACVs.

There was no significant difference in the distribution of SPs across the 4 Australian states from which isolates were collected. We have previously shown that isolates with SP13 and SP14 were isolated as early as 2000 [8]. This suggests that they were circulating for at least 8 years before causing the epidemic that currently exists throughout Australia.

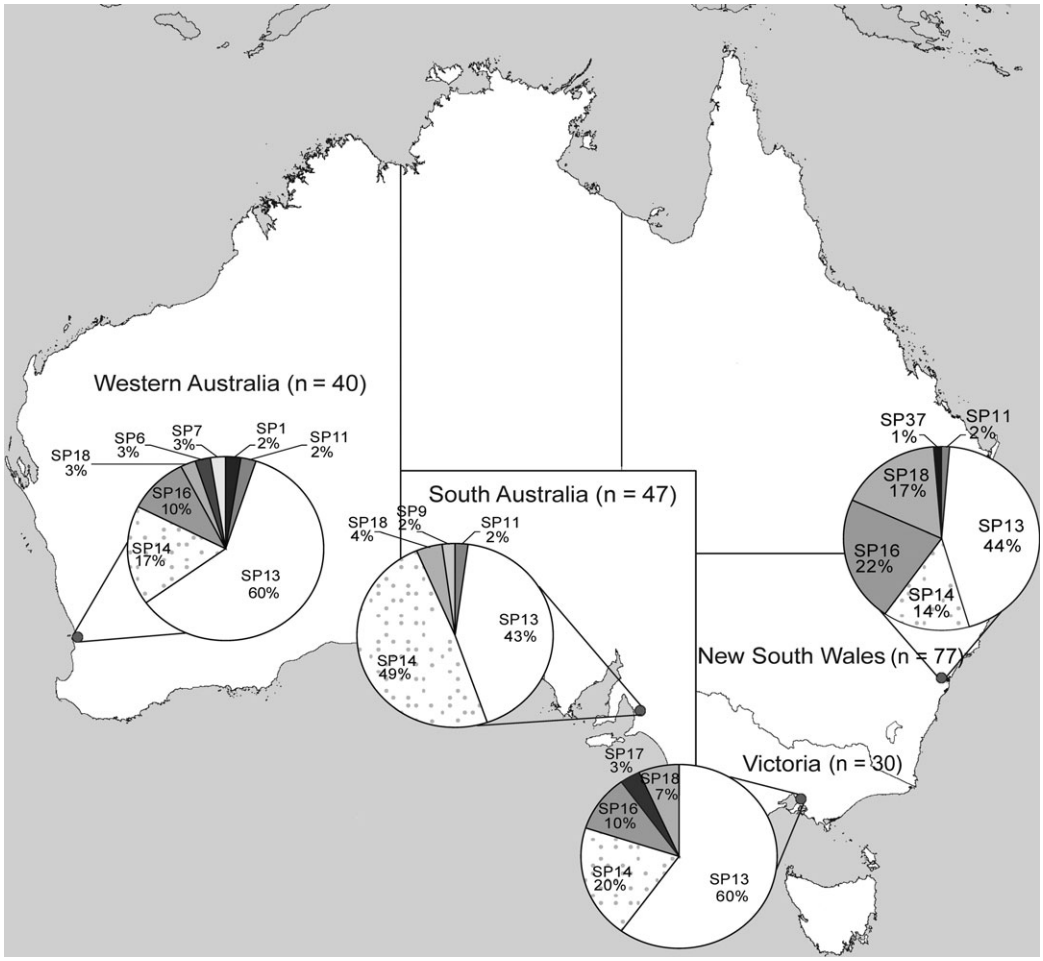

Figure 1. Distribution of epidemic isolates recovered during 2008–2010, by single nucleotide polymorphism (SNP) profiles (SPs), across the capital cities of 4 states in Australia.

The combination of *prn* and *ptxP* alleles is of particular importance. The isolates were divided into 4 types: *prn2-ptx3*, non-*prn2*–non-*ptxP3*, *prn2*–non-*ptxpP3*, and non-*prn2*–*ptxp3*. The latter 2 had a low overall frequency of 4%. However, 84% of the isolates were *prn2-ptxP3* (Figure 2*C*). Previous immunological evidence clearly has shown that *prn2* has an advantage against ACV immune selection pressure [11, 12], while *ptxP3* has been found to be associated with higher virulence on the basis of hospitalization and case mortality data [10]. Although isolates from this study were not typed for *ptxA*, it should be noted that, on the basis of data from our previous study, all cluster I–IV strains carry *ptxA1*. This means that there is an allelic mismatch between the currently circulating (SNP cluster I) *ptxA* allele, *ptxA1*, and the ACV allele, *ptxA2*. Increased production of PT promoted by *ptxP3* may compound the effect of the antigenic difference between the products of different *ptxA* alleles in reducing ACV-induced protection. Clonal expansion of *B. pertussis* strains carrying *ptxP3* has also been associated with recent epidemics of pertussis in several European countries [1, 13]. Strains carrying *prn2*, some of which presumably also carry *ptxP3*, have been found or have increased in frequency in China [14] and other countries [13] where WCVs are used. It remains to be seen whether these strains will displace the others in WCV-immunized populations.

The *prn2-ptxP3* isolates have the potential not only to evade the protective effects of ACV but also to increase disease severity as a double act of *B. pertussis* adaptation. Therefore, vaccine-induced selection could contribute to the expansion of cluster I, specifically SP13 and SP14, because of the presence of both *prn2* and *ptxP3*. These 2 SPs have swept across Australia during the epidemic period. Interestingly, they have also been found in other countries [8], suggesting that they have the potential to cause epidemics elsewhere. Therefore, it is very important to monitor the prevalence of these clones globally.

Our previous study showed that cluster II decreased in frequency after introduction of ACV [8]. Current data suggest

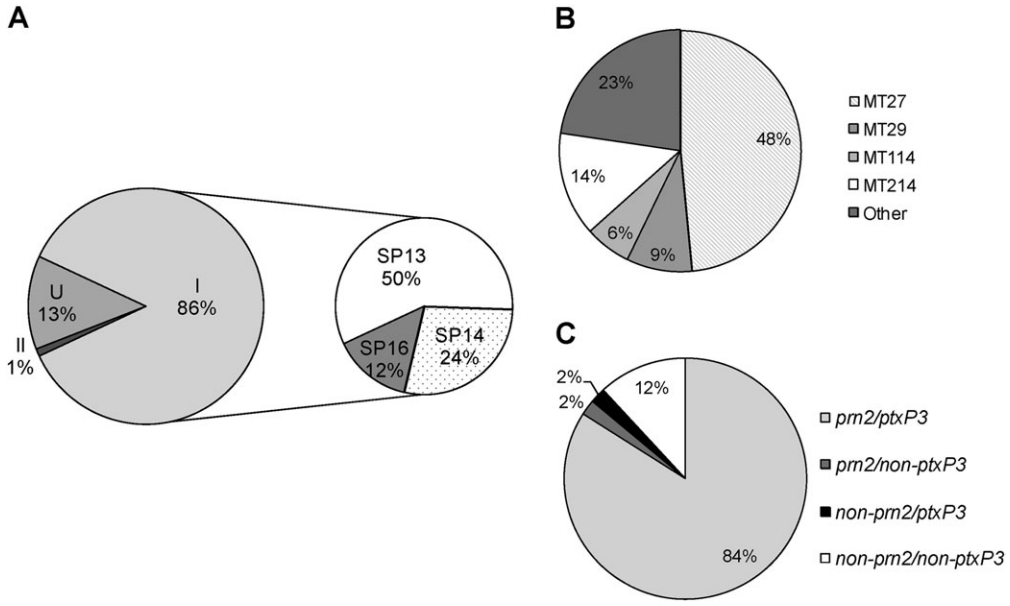

Figure 2. Distribution of single nucleotide polymorphism (SNP) clusters and profiles, multilocus variable number of tandem repeats analysis types (MTs) and *prn-ptxP* alleles among epidemic isolates recovered during 2008–2010 in Australia. *A*, Distribution of isolates by SNP clusters (I, II, and U [unclustered]) and SNP profiles (SPs) within cluster I. *B*, Distribution of isolates by MTs, with the top 4 MTs shown. *C*, Distribution of *prn* and *ptxP* types.

that this cluster is on the verge of being completely replaced by cluster I. Cluster IV also increased after introduction of ACV in our previous study [8]. However, it was not observed in this more recent epidemic in the 4 states we sampled. More samples from the other states may help to explain the deficiency of cluster IV strains in this study. Furthermore, this study lays the foundation for future studies to determine any correlation between genotypes of *B. pertussis* isolates and both disease severity and vaccination history.

In conclusion, the prolonged epidemic in Australia that began in 2008 was predominantly caused by SPs from cluster I carrying *prn2* and *ptxP3*, which have been circulating in this country since at least 2000. There may be other unknown factors contributing to the increase of cluster I strains, but they appear to have a selective advantage over strains carrying non-*prn2* and non-*ptxP3* alleles under the pressure of ACV vaccination. Therefore, clones carrying *prn2-ptxP3* have the potential to cause epidemics in other countries covered by ACV with formulations similar to those used in Australia and should be monitored locally and globally.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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