1. Background

In the 19th and the first half of the 20th centuries, childhood deaths from many infectious diseases, including measles, diphtheria and poliomyelitis, were common. Since then vaccines have dramatically reduced the rates of many childhood infections, deaths from vaccine-preventable diseases (VPDs) are now very rare in the developed world and their incidence has fallen sharply in many developing countries over the past 10 - 20 years because of successful immunization programs.

Nevertheless, there are still 2 - 3 million childhood deaths each year, worldwide, from VPDs. Even in countries with consistently high immunization rates, cases of some VPDs, which have been virtually eliminated, still occur occasionally. Control of some VPDs – influenza and pertussis, for example - remains elusive, because of less-than-ideal vaccines.

In Australia, the first dramatic change attributable to immunization, in the incidence of an infectious disease, began when diphtheria toxoid introduced into school-based and infant immunization programs in the 1930s and early 1940s, respectively, notifications plummeted and deaths from diphtheria fell from about 4000 during 1926 – 1935, to only 44 between 1956 and 1965. (Figure 1)

Similarly, deaths from pertussis fell progressively after the introduction of whole cell pertussis vaccine in the 1940s. Salk (injected) and later Sabin (oral) polio vaccines, introduced in 1950s and 1960s, respectively, halted the catastrophic polio epidemics that had occurred, in Australia, during the preceding two decades. Measles immunization, commencing in 1969, gradually led to disappearance of the regular 2-3 yearly measles epidemics, when virtually every susceptible child was infected and some died. Rubella immunization has almost eliminated one of the most devastating causes of congenital infection; mumps and varicella vaccines have reduced the incidence these common childhood infections and their uncommon, but potentially serious complications to low levels. The incidence of invasive disease due to *Haemophilus influenzae* type b
(Hib), *Neisseria meningitidis* type C and *Streptococcus pneumoniae* - the commonest causes of childhood meningitis – have also fallen to very low levels since the introduction of effective conjugate vaccines.

Tens of thousands of deaths of Australian children were prevented, during the 20th century, by immunization† (Table 1) and the benefits have been supplemented by the introduction of newer vaccines. Rotavirus vaccine has reduced hospital admissions and deaths from infant diarrhea, hepatitis B and human papilloma virus vaccines have protected thousands of adults from liver and cervical cancer, respectively, and many others have prevented infections in travellers or people who are at risk of exposure to exotic infections.

**Table 1. Deaths from diseases commonly vaccinated against, Australia 1926-2000 (from McIntyre et al2).**

<table>
<thead>
<tr>
<th>Period</th>
<th>Diphtheria</th>
<th>Pertussis</th>
<th>Tetanus</th>
<th>Poliomyelitis</th>
<th>Measles†</th>
<th>Population estimate</th>
</tr>
</thead>
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<tr>
<td>1926–1935</td>
<td>4073</td>
<td>2808</td>
<td>879</td>
<td>430</td>
<td>1102</td>
<td>6 600 000</td>
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<tr>
<td>1936–1945</td>
<td>2791</td>
<td>1693</td>
<td>655</td>
<td>618</td>
<td>822</td>
<td>7 200 000</td>
</tr>
<tr>
<td>1946–1955</td>
<td>624</td>
<td>429</td>
<td>625</td>
<td>1013</td>
<td>495</td>
<td>8 600 000</td>
</tr>
<tr>
<td>1956–1965</td>
<td>44</td>
<td>58</td>
<td>280</td>
<td>123</td>
<td>210</td>
<td>11 000 000</td>
</tr>
<tr>
<td>1966–1975</td>
<td>11</td>
<td>22</td>
<td>82</td>
<td>2</td>
<td>146</td>
<td>13 750 000</td>
</tr>
<tr>
<td>1976–1985</td>
<td>2</td>
<td>14</td>
<td>31</td>
<td>2</td>
<td>62</td>
<td>14 900 000</td>
</tr>
<tr>
<td>1986–1995</td>
<td>2</td>
<td>9</td>
<td>21</td>
<td>0</td>
<td>32</td>
<td>17 300 000</td>
</tr>
<tr>
<td>1996–2000</td>
<td>0</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>18 734 000</td>
</tr>
</tbody>
</table>

† Excludes deaths from subacute sclerosing panencephalitis.

* Indicates decade in which community vaccination started for the disease.

2. Current status of some vaccine preventable diseases in Australia.

2.1 Diphtheria

Although diphtheria was rare in Europe, North America and Australasia by the 1960s, small outbreaks and sporadic cases occurred in Australia, until the 1990s. Twenty-three cases including one death were notified in 1991-2, mainly in the Northern Territory among Indigenous adults†. On a much larger scale, there was a massive diphtheria epidemic in the 1990s, in Russia and the Newly Independent States, following the break up of the Soviet Union, where immunization rates, previously, had been high. Vaccine supplies failed when workers were unpaid and access to basic medical services was hindered by social disruption caused by conflict and mass migration. Diphtheria spread from unimmunized children to adults with waning vaccine-induced immunity, including soldiers, who often carried it from one region to another. Between 1990 and 1997, there were 150,000 cases and 5000 deaths3. This prolonged outbreak is now under control, but it was a stark reminder of the risk of re-emergence of
VPDs when immunization programs fail.

In April 2011 a young woman died, in Brisbane, from diphtheria. Her partner had recently returned from Papua New Guinea with a sore throat and, when she developed similar symptoms, she was assumed to have a streptococcal throat infection. She did not respond to treatment and died from toxigenic diphtheria. She had never been immunized. On the other hand, her partner had been fully immunized. Presumably he had had pharyngitis due to Corynebacterium diphtheriae but was protected from the effects of toxin by vaccine-induced immunity.

Diphtheria remains endemic in many countries, including some in our region, and a potential risk to unimmunized travellers or, as in this recent case, their unimmunized contacts. Immunization protects against toxigenic disease, but not necessarily against localized throat or skin infection.

2.2 Pertussis

Pertussis typically occurred in regular large outbreaks every 2-4 years, with significant morbidity and mortality, mainly in young children. After pertussis vaccination was introduced in the 1940s, notifications and deaths from pertussis fell dramatically (Figure 2). There were 1700 deaths from pertussis in Australia, between 1936 and 1945, compared with fewer than one per year, on average, over the past 20 years, virtually all in young (<6 months), unimmunized infants.

![Figure 2. Pertussis notifications in Australia from 1917 to 2007. (from: Chiu et al. 2010)](image)

Control of pertussis remains fragile. In the United Kingdom, in the 1970s, public concern about a reported (but unproven) association between whole cell pertussis vaccine and serious neurological sequelae led to a fall in pertussis immunization rates, followed by significant increases in the number of cases and deaths (Figure 3). Even with high immunization rates, regular outbreaks still occur and, although still much smaller than before, their size and duration is increasing in many countries.
In Australia, in the 1990s, pertussis IgA antibody testing began to be widely used for diagnosis. Despite its limitations, it is more likely, than culture, to be positive in older children and adults with pertussis, in whom the disease is often atypical and not considered until 2 or 3 weeks after the cough begins. This resulted in increased awareness of atypical infection, associated with waning immunity, as a potential reservoir of infection of unimmunized infants and the need for boosters every 10 years.

Concern about the relatively high reactogenicity of whole cell vaccines, especially in older children and adults, led to their being replaced in many countries (including Australia in 1999) with acellular vaccines containing purified antigens. The acellular vaccine used in Australia contains pertussis toxin, filamentous haemagglutinin and pertactin (others also contain agglutinogens), which can be safely given as booster at 4 and 15-17 years of age.

Pertussis rates are apparently increasing, in Australia, despite high infant immunization rates. From 2002-2008, there were 5,000-10,000 notifications annually\(^4\), compared with >30,000 per annum in in 2009-2011 (http://www9.health.gov.au/cda/Source/Rpt_3.cfm). Some of this increase probably reflects increased awareness and diagnostic testing, due to the more widespread availability of PCR, which is more sensitive than culture and less invasive than serology. However, there has also been an increase in hospital admissions of children <12 months old and occasional deaths occur in infants aged 0-4 months, although the overall mortality rate is comparable with that in countries where notification rates are much lower. (http://ncirs.edu.au/news/past-news-events/Day%2001/McIntyre-Is-Australia-world-capital-PertussisWS-25_26Aug11.pdf)

It is plausible that the recent increase in the incidence of pertussis is at least partly related to the change from whole cell to acellular vaccine. The latter causes fewer adverse events and is well tolerated by adults, but provides less
prolonged, narrower spectrum\(^a\) immunity. There is evidence that the current, circulating strains of *Bordetella pertussis* have changed since the introduction of acellular vaccine and they express antigens that differ from those contained in the vaccine\(^7\).

### 2.3 Poliomyelitis

Salk (injected) and Sabin (oral) polio vaccines were introduced in 1956 and 1966 respectively. Catastrophic polio epidemics caused more than 1000 deaths, between 1946 and 1955, and left thousands of survivors handicapped from paralysis, including some who were ventilator-dependent for the rest of their lives. Since the mid-1960s there have been only 4 deaths from polio in Australia and no notified cases of wild type polio for more than 30 years. Australia was declared polio-free in 2000. In 2007, an imported case occurred in a Pakistani student, in Melbourne, who developed paralytic polio, despite having been immunized as a child, after returning from a visit to Pakistan\(^8\). This is a reminder of the need for maintenance of high immunization rates and of surveillance of acute flaccid paralysis, at least until the disease is eradicated worldwide.

Because of the small risk of paralysis (less than 1 per million doses) from polio vaccine strains, which is now considerably greater than that of wild polio, the live attenuated oral polio vaccine was replaced, in 2005, with the inactivated vaccine\(^2\).

Until recently, the global polio eradication program appeared to be on track, with fewer than 500 cases, worldwide in 2001, but its final goal remains elusive. Since 2006, polio has been endemic in only four countries: Nigeria, India (Uttar Pradesh and Bihar), Pakistan and Afghanistan, but periodically “leaks” into nearby countries (Figure 4). For example, although China had been free of polio for 10 years, there was an outbreak in September 2011, probably resulting from importation from Pakistan. Transmission has occurred or been recently re-established in Angola, Chad, the Democratic Republic of Congo and the Sudan. ([http://www.polioeradication.org/Infectedcountries.aspx](http://www.polioeradication.org/Infectedcountries.aspx)): On 13 January, 2012, India reached a major milestone - a 12-month period without a case of polio being recorded. A single case was reported in 2011 in West Bengal. ([http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx](http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx)). The current WHO goals for polio eradication are: cessation of transmission of wild polio by the end of 2012 and initial validation of this goal by the end of 2013. If the program remains on track, polio will be the second communicable disease, after smallpox, to have been eliminated, globally, because of the availability of safe and effective vaccines.

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\(^a\)Whole cell vaccines contain numerous poorly defined antigens, in addition to the main “protective” antigens. These additional antigens were responsible for much of the excess reactogenicity, but also probably acted as adjuvants, leading to enhanced immune responses to specific protective antigens (probably including different alleles from those in the vaccine strain, such as those in *Bordetella pertussis* strains that are currently circulating).
2.4 Measles

Measles vaccination of infants began in Australia in 1969 and gradually led to disappearance of the regular 2-3 yearly measles epidemics during which virtually every susceptible child was infected, many were admitted to hospital with severe disease, encephalitis or secondary bacterial complications, such as pneumonia, and a significant number died. In the 1980s and ‘90s, measles outbreaks occurred intermittently because vaccine uptake had plateaued at a level that provided insufficient herd immunity to prevent spread of such a highly contagious disease among susceptible individuals.

A national serosurvey in 1997-8 showed that up to 15% of children and young adults were susceptible to measles, suggesting that the risk of a major epidemic was high. During the Australian Measles Control Campaign, in 1998, more than 90% of primary school children were given measles, mumps and rubella (MMR) vaccine. Parents of preschool children, identified by the newly established Australian Childhood Immunization Register (ACIR) as being behind with scheduled immunizations, were sent reminders and immunization rates in this group increased.

A second serosurvey after the campaign showed that fewer than 2% of children in the age groups targeted were susceptible. Since then, infections in these age groups have been uncommon. Small outbreaks, particularly among young adults, originating from index cases acquired overseas, have continued to occur (Figure 5a), but have generally been confined to immediate contacts of the index case, without secondary spread. In 2008 a case was made that measles should be declared eliminated in Australia. However, larger outbreaks occurred in 2011; between January and September 136 measles cases were notified in Australia, compared to 70 in 2010 (Figure 5b). Most of those affected were

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8 Measles elimination is defined as interruption of transmission in a sizeable geographic area but, because of the continued threat of reintroduction of the virus, vaccination needs to be continued. (Cutts, et al)
unvaccinated schoolchildren but they included 9 children less than one year old. These and recent outbreaks in other countries have jeopardized the goal of measles elimination, by 2012, in the WHO Western Pacific Region (http://www.medicalobserver.com.au/news/measles-cases-double-in-past-year).

2.5 Invasive Haemophilus influenzae type b (Hib) disease

Invasive disease due to Haemophilus influenzae type b occurs predominantly in children <5 years old. It was the commonest cause of childhood meningitis and associated with significant mortality and longterm neurological sequelae. The incidence of invasive Hib disease (including pneumonia and meningitis), was particularly high among indigenous children <2 years old in Australia and other Western countries. Epiglottitis, which occurred in a somewhat older age group, was rarely associated with long-term sequelae but could cause upper airway obstruction and death\textsuperscript{14}.

Hib vaccines were the first of several conjugate vaccines against invasive bacteria, of which polysaccharide capsules are the major virulence factor. Children <2 years old, cannot mount an effective immune response against polysaccharides, but if the polysaccharides are conjugated to a protein, the conjugate stimulates a protective immune response. Several Hib vaccines have been available in Australia and immunogenicity varies, depending on the protein used for conjugation\textsuperscript{15}.

The annual rate of Hib disease fell from about 500-600/100,000 before the introduction of the first Hib conjugate vaccine, in 1993, to fewer than 50/100,000 since 1995\textsuperscript{5,15} (Figure 6). The Hib vaccine has been highly successful, in part because type b is the only one of the six H. influenzae capsular serotypes that commonly causes invasive disease. Contrary to early concern, the use of Hib vaccine has not been associated with an increase in Hib disease in older children or replacement by nonencapsulated Hi or other serotypes (H. influenzae types a and f infections are uncommon).

In 2006-7 (2 years), 39 cases of invasive Hib disease were notified in Australia; 21 were in children <5 years old and none died. Most cases of invasive Hib
disease occur in unimmunized children\textsuperscript{4} or in elderly or immuno-compromised people.

![Graph showing incidence of meningococcal disease](image)

**2.6 Meningococcal disease**

Meningococcal disease, in Australia, is usually due to either *Neisseria meningitidis* serogroup B or C. (serogroup A classically causes epidemics in the so-called “meningitis belt” of sub-Saharan Africa and in Asia; serogroups Y, W135 and others are relatively uncommon). The most serious manifestations are meningococcaemia, often associated with septic shock, and meningitis; both cause significant morbidity and mortality.

Like Hib disease, meningococcaemia is most common in <5 year-olds but there is also a secondary peak among adolescents and young adults (Figure 7). It has a seasonal pattern, with peaks in late winter and spring (Figure 8).

![Graph showing age distribution of meningococcal disease](image)

The incidence of meningococcal disease has fluctuated in Australia, but was relatively low during the latter half of the 20\textsuperscript{th} century. However, it began to increase in the 1990s (Figure 9). In recent years, serogroup B is responsible for most sporadic disease in Australia. Previously serogroup A was responsible for large outbreaks, particularly among Indigenous populations. The incidence of serogroup C fluctuates over long periods and was rare in Australia until the 1980s, when its emergence was first recognised\textsuperscript{16}. By the early 2000s was responsible for 30-40\% of cases of invasive meningococcal disease, although its
incidence varied in different States and Territories. It was largely responsible for the overall increase in the rates of meningococcal disease, nationally.\textsuperscript{17}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Meningococcal disease notifications and deaths in Australia (1915-2005) (from Patel\textsuperscript{16})}
\end{figure}

A tetravalent polysaccharide vaccine (against serogroups A, C, Y and W125) has been available for many years but, like other polysaccharide vaccines, is not immunogenic in infants. There is no comparable serogroup B vaccine because the similarity between its polysaccharide and sialic acid, a component of human cells, means that it is not recognized as a foreign antigen. Unique, highly targeted “vesicle” (outer membrane protein) vaccines, which are effective against specific outbreak strains, have been developed, to combat prolonged, but localized, outbreaks in several countries\textsuperscript{17}.

In 2003, a meningococcal serogroup C conjugate vaccine was introduced into the routine infant schedule in Australia and was offered to all children and adolescents aged 1-19 years as “catch-up” during the first year. Since then there has been a fall in the overall incidence of meningococcal disease largely due to a much smaller proportion of serogroup C disease, while the numbers of serogroup B infections have remained relatively stable (Figure 10). In 2010, 85\% of \textit{N. meningitidis} isolates referred for typing were serogroup B and only 8\% serogroup C\textsuperscript{18}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Changes in numbers of cases due to different meningococcal serogroups (from Chui \textit{et al})}
\end{figure}

Note that, until the late 1990s, the majority of isolates were not serogrouped. Serogroup C disease has fallen since the introduction of conjugate meningococcal vaccine in 2003, mainly in the vaccine target group, with some herd effect in older age-groups. The numbers of serogroup B cases, annually, have remained fairly steady.
2.7 Invasive pneumococcal disease.

Invasive pneumococcal disease is more complex and more common than either Hib or meningococcal disease. There are more than 90 serotypes of *Streptococcus pneumoniae*, many of which can cause invasive disease, which varies in severity from unlocalised, often relatively benign bacteraemia to life-threatening pneumonia or meningitis. It is more common in winter and the peak incidence often coincides with influenza and other respiratory disease outbreaks. Like the other two common invasive bacterial infections it is most common in the very young, but there is another major age-peak in the elderly (Figure 11), in whom it is also the commonest cause of non-bacteraemic pneumonia (often not recognized or recorded as invasive pneumococcal disease).

A relatively small number of the >90 serotypes, cause the majority of cases of invasive pneumococcal disease in the absence of immunization. A 23-valent, polysaccharide vaccine has been available, but not widely used, for many years. It is ineffective in the very young and relatively poorly immunogenic in the elderly and immune-compromised for whom it is most needed. More recently, the seven most common so-called “paediatric” serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), which were responsible for >85% of infections in children in most Western countries, and were often antibiotic resistant were included in the 7-valent pneumococcal conjugate vaccine. This was introduced in Australia, initially for Indigenous children and those with underlying risk factors, in 2003, and then into the routine infant immunization schedule in 2005.

Since then there has been a sharp fall in the incidence of invasive pneumococcal disease, mainly due to the decrease in disease due to vaccines serotypes, in the target age-group (<5 years), with a similar but less marked effect in the elderly, as a result of herd effect. The fall in rates of pneumococcal disease among Indigenous children was less dramatic and plateaued after about 2 years of conjugate vaccine use (Figure 12, above). This is largely because these children are susceptible to a wider range of serotypes than included in the vaccine, including some included in newer vaccines.
The overall decrease in the rate of invasive pneumococcal disease has been partly off-set by an increase in disease due to non-vaccine serotypes, particularly serotype 19A (Figure 13), which has increased in many parts of the world, following the use of conjugate vaccine.

Serotype 19A has a high frequency of penicillin resistance; in some geographic areas (such as North America) this is predominantly high level resistance (MIC >2mg/L) whilst in others (such as Australia) it is mainly low level/intermediate resistance (MIC 0.12-1 mg/L), depending on which clone(s) has/have either expanded or emerged under pressure of vaccine-induced immunity.

The 7-valent conjugate vaccine was replaced, in early 2012 in Australia, by a 13-valent vaccine (which contain the same serotype antigens as the 7-valent vaccine plus 1, 3, 5, 6A, 7F, 19A). It is anticipated that this will further reduce the incidence of invasive pneumococcal disease in young children, including Indigenous children, in whom the rates remain quite high, despite high vaccine uptake. The extent of its effect in high-risk groups, including Indigenous people, the elderly and the immuno-compromised, remains to be seen, given the plasticity of the *S. pneumoniae* genome and its great propensity for recombination, in response to selection pressure from vaccine-induced immunity or antibiotic use.

**Conclusions**

Safe and effective vaccines have saved the lives of millions of children, worldwide and will continue to do so long as immunization programs are maintained. The acquisition costs of the well-established childhood vaccines have fallen to levels that make them affordable for the most impoverished countries, some of which, with varying degrees of assistance from international nongovernment organizations, have established the health infrastructure required for vaccine delivery. This, in turn, has major benefits for health service delivery in general.

Many new vaccines have become available, recently, others are under development and new technology will make others feasible in future. There are still some major gaps: effective vaccine against the “big three” global diseases, HIV, TB and malaria, remain elusive. Some existing vaccines are less effective...
than we would like: influenza vaccines have to be changed regularly and their manufacture remains relatively primitive; newer pertussis vaccines now have fewer side-effects but are less immunogenic. Some communicable diseases are unlikely to ever be controlled by immunization, because of pathogen, host or population characteristics.

Advances in vaccine technology and new delivery systems will overcome many of these problems but some barriers to successful development and delivery of vaccines are not technical, but social, economic, ethical or political. These include the cost of new vaccine development, especially for vaccines against diseases that mainly occur in poor countries; the very high standards of safety required, which leads to very low tolerance of risk by manufacturers; the difficulties and costs involved in vaccine trials, especially in developing countries and for relatively uncommon diseases; and complacency, on the part of parents, governments and the general public, about the need for infectious disease prevention – now that they have been overtaken by chronic non-communicable diseases as major causes of death, coupled with concerns about hypothetical adverse effects of the use of increasing numbers of vaccines.
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