Australia’s contribution to global immunisation

Abstract

Objective: To review Australian contributions to global immunisation. Approach: We summarise Australian scientific and program contributions to vaccines and global immunisation, describe key developments and strengths in Australia’s national immunisation program, and outline how both of these can link with Australia’s increasing international development budget to build Australia’s future contribution to global immunisation.

Conclusions: Australian contributions to vaccines and immunisation have been substantial, and Australia offers a range of good practices in its domestic and development approaches. There are major opportunities to build on this strong track record. These include committing to help roll out important new life-saving vaccines against pneumococcal disease, rotavirus and human papilloma virus (HPV) to the children who need them most, but whose communities can least afford them.

Implications: Australia is one of a few countries expanding their aid budgets towards 0.7% development assistance and other development commitments. Given the importance of immunisation to health gains, Australia is well placed to expand its investment in immunisation within its development portfolio. The GAVI Alliance is the best-established global mechanism to do this. Additionally, however, Australia could harness other national and regional mechanisms to support low and middle-income countries, thereby complementing GAVI’s focus and global needs.

Key words: Australia, immunisation programs, international immunisation, Australian national immunisation program

Tilman A. Ruff, Kate Taylor
Nossal Institute for Global Health, The University of Melbourne

Terry Nolan
Melbourne School of Population Health, The University of Melbourne

Despite significant contributions to the science of vaccines and immunisation programs, and strengths in national programming and support for regional programs, Australia’s role in global immunisation is relatively undocumented and unrecognised. We know of no published work addressing Australia’s contribution to global immunisation, and therefore set out to provide such a paper.

Approach

We first summarise the important role and potential of vaccines as tools for health, equity and development. Second, we describe Australian contributions to vaccine-relevant basic science; vaccine research and development; and immunisation program policy, implementation and leadership. Third, we outline developments and achievements in Australia’s national immunisation program which provide a body of expertise, experience and leadership which serves as a useful resource beyond Australia. Fourth, we examine the Australian Government’s international development assistance for immunisation. Finally, in the context of a growing government international development assistance budget, we recommend how these elements may be combined and built on to develop Australia’s future contributions to global immunisation.

The genesis of this paper was a policy brief commissioned by the GAVI Alliance in 2011 to document Australian contributions to global immunisation, encourage this substantial and diverse legacy to be built on, and identify some ways in which this might be done. We could find no previous publication addressing this topic, and so sought to publish a paper readily accessible to Australian public health practitioners and policymakers.

We have not undertaken a systematic review or a comprehensive account of all Australian contributions to global immunisation; rather we have documented our collective perspective on the highlights. We sought input and critical comment from seven diverse senior Australian immunisation leaders, selected on the basis of a manageable number of willing prominent experts who, together with the authors, provided expertise in:

• vaccine basic and clinical science;
• Australian immunisation policy and programs at national and state/territory level;
• Australian regulatory and technical advisory processes for vaccines;
• immunisation programmes in developing countries;
• international organisations key in global immunisation, particularly WHO, UNICEF and the GAVI Alliance; and
• the vaccine industry and public/private partnerships in immunisation.

Vaccines remain critical health and development tools

Immunisation support is one of the most proven and cost-effective investments in global health, human security and international development. It has long been recognised as a cornerstone of health systems and represents an excellent access point for strengthening...
Communicable Disease Australia and global immunisation

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health systems based on the goal of universal coverage.

Vaccines’ track record in health economics and public health impact is enormous, including through programs to eradicate smallpox, and control measles, diphtheria, tetanus, pertussis, rubella, Haemophilus influenzae type b (Hib), meningococcal disease, yellow fever, Japanese encephalitis and other serious diseases. It is estimated that immunisation averts 2.5 million deaths each year, and many more cases of disease and disability.1 Vaccines are critical to the achievement of Millennium Development Goal 4 (to reduce by two-thirds, between 1990 and 2015, the mortality rate of children under 5 years), as well as to reaching other internationally agreed targets, such as the eradication of polio. Beyond the MDG 2015 target, vaccines offer continued promise of saving the lives of millions globally, and this promise will only grow as needed vaccines against malaria, dengue and HIV come to fruition.

As important available vaccines remain insufficiently used, there is an opportunity for many countries – rich and poor – to increase their support for immunisation. The approaches underpinning immunisation success – focusing on performance, sustainability and partnership – align well with Australia’s aid philosophy.

Australia’s contributions to vaccine science

Australians have made scientific contributions disproportionate to their number. Breakthroughs range from discoveries about the way our immune system works, through to the pathogens that cause human, animal and plant diseases and how they do this – understandings fundamental to the identification of possible vaccine components, and the development and evaluation of candidate vaccines.

Australia started producing smallpox vaccine in 1847, and the national vaccine and biologicals manufacturer, the Commonwealth Serum Laboratories (CSL), was established in 1916.2 In 1906, Thomas Bancroft in Brisbane demonstrated that mosquitoes transmitted dengue fever.3 Many Australian vaccine contributions followed.4 Probably the best known was by Frank Macfarlane Burnet of the Walter and Eliza Hall Institute (WEHI) in Melbourne whose work formed the foundation for future genetic and molecular biological discoveries in microbiology and later immunology.5 Burnet discovered the oral transmission of poliovirus, described the epidemiology of herpes simplex, and in the 1930s and 1940s discovered much about influenza.6 He pioneered growing flu virus in chicken eggs, still the backbone of vaccine production today, as well as making other discoveries relating to the basic science and epidemiology of various viral infections.

At about the same time, Norman McAlister Gregg, a Sydney ophthalmologist, discovered that rubella caused serious birth defects,7 which eventually led to the vaccine that, in turn, has been responsible for the interruption of endemic transmission of rubella throughout the Americas since 2009,8 and potentially in Australia.

Such results encouraged the founding new organisations – including the Queensland Institute of Medical Research (Brisbane), Institute of Medical and Veterinary Science (Adelaide), John Curtin School of Medical Research (Canberra), Royal Children’s Hospital and Murdoch Childrens Research Institute (Melbourne), Millennium Institute (Sydney), Burnet Institute (Melbourne), and TVW/Telethon Institute (Perth). These have grown into national and global resources for science and training (see Table 1). Their discoveries of viruses and thence vaccines are notable, even though for some vaccines their full impact is yet to be realised, particularly in the most vulnerable populations in the developing world. One is Ian Frazer’s work on human papilloma virus (HPV) that led to the first vaccine against cervical cancer,9 which kills about 260,000 women globally each year.10

Another began in 1973, when Ruth Bishop and colleagues discovered a new group of viruses, the rotaviruses, which infect over 95% of children by 5 years of age, causing more than 100 million episodes of illness and about 500,000 deaths each year, mostly in poor countries.11 Today there are safe and effective vaccines, though not yet widely used in poor countries. Work continues in collaboration with Indonesia’s national vaccine producer BioFarma to produce a low-cost vaccine for use in the developing world.12

While ongoing vaccine research cannot be adequately addressed here, it is appropriate to note that world class vaccine-relevant basic and clinical research is being undertaken in Australia in a number of

Table 1: Additional selected Australian immunisation-relevant scientific contributions.

- In 1918, Breini and Cleland established a viral cause for Murray Valley Encephalitis.2 In 1952, French identified the causative arbovirus.2
- R. Doherty, I. Marshall and colleagues discovered and characterised some 70 arboviruses, including a number that cause encephalitis in humans.2
- Pope linked Epstein-Barr virus to Burkitt’s lymphoma.3
- P. Doherty and Zinkernagel elucidated key immunological factors enabling organ transplantation, based on earlier virological research – winning the Nobel Prize in Medicine in 1996.3
- In the 1980s, Marmion developed the world’s first (and still only) licensed vaccine against Q fever.41 The causative bacterium Coxiella burnetti had been discovered by Derrick and Burnet in the 1930s.
- Lawrence and colleagues developed a toxoid vaccine against clostridial necrotising enteritis (pigbel).42 In the 1960s and 1970s, this was the most common cause of death in children over the age of 1 year in hospitals in the highlands of PNG.
- Gust led a team which isolated a strain of hepatitis A virus (HM175) used to produce the world’s first vaccine against hepatitis A.43
- Burrell characterised the hepatitis B virus genome. This led to replacement of the first generation of plasma-derived HB vaccines by recombinant vaccine produced in yeast cells, the first vaccine borne of modern molecular biology.
- B. Marshall and Warren received a Nobel Prize for their discovery that Helicobacter pylori was the most common cause of peptic ulcers and gastric cancer.
- Shann has been a consistent international advocate for better understanding of the science and program implications of non-specific effects of vaccines.44

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areas, including in HIV, influenza, pneumococcal proteins, middle ear infections, malaria, Group A streptococci and peptic ulcers.

**Putting vaccine science into practice**

Australian contributions to global immunisation include policy, program development and implementation activities. A proud moment was Frank Fenner’s role in the world’s greatest immunisation achievement – arguably the greatest public health achievement. From 1969 Fenner, an expert on pox viruses, played a leading role in the WHO Intensified Smallpox Eradication Campaign, and from 1977 chaired the Global Commission on the Certification of Smallpox Eradication. On 5 May 1980, he announced the eradication of smallpox to the World Health Assembly, later penning the definitive account, a monumental 3.5 kg monograph.

Gus Nossal led the WEHI as an outstanding immunologist. Building on his decade of leadership of the WHO Scientific Advisory Group of Experts on immunisation, he embraced a second career as a global health advocate, championing unprecedented investment in immunisation by the Bill and Melinda Gates Foundation (BMGF) to create the GAVI Alliance. Ian Gust’s distinguished leadership included research seminal to the first hepatitis A vaccine and understanding the regional epidemiology of hepatitis B (HB) and influenza; key support through CSL for the development of HPV vaccine; and program leadership through WHO, UNICEF, BMGF, and the International AIDS Vaccine Initiative. In the mid-1980s, Gust was a driving force in building early experience with HB vaccine, showing that inclusion of HB vaccine in routine immunisation programs was feasible, did not reduce coverage of other vaccines, and was highly effective in reducing infection in children, including by transmission from an infected mother to her infant. These programs were the first, through competitive international tender, to procure HB vaccine for less than US$1 per dose. Subsequently, the World Health Assembly (1992) and WHO (1994) recommended universal HB immunisation and inclusion of HB vaccine in all national immunisation programs by 1997, the first new vaccine to be universally recommended for inclusion in WHO’s Expanded Program of Immunisation since its inception in 1974. They set a global target of 80% reduction in new chronic infections among children by 2001.

As GAVI rolls out its pilot Advanced Market Commitment (AMC) for pneumococcal vaccines, it is worth noting Australian contributions towards those vaccines. Thirty years ago in Papua New Guinea, Australian doctors led by Ian Riley, using a polyaccharide vaccine, first demonstrated the major life-saving potential of pneumococcal vaccines for adolescents and adults, and subsequently, with Deborah Lehmann and Mike Alpers, their life-saving potential for infants. Around the same time, Frank Shann and colleagues demonstrated the importance of pneumococci and non-typeable *Haemophilus influenzae* as causes of childhood pneumonia, highlighting the potential for vaccines to prevent this most frequent cause of deaths in children worldwide. Australian paediatrician Kim Mulholland has been key in the large pneumococcal conjugate vaccine efficacy trials in the Gambia, South Africa and the Philippines (as well as the Hib vaccine efficacy trials in the Gambia and Indonesia).

Of course, other valuable Australian contributions to global immunisation occur embedded within wider programs, such as Jim Tulloch’s work in WHO to oversee the development of the Integrated Management of Childhood Illness (IMCI) strategy.

**Australia’s immunisation achievements at home**

Australia was among the first countries to introduce vaccines against polio and measles; in 2007, Australia was the first country to fund HPV vaccine for all females aged 12 to 26 years. By 2011, 3-dose coverage was around 70%, currently the highest coverage of young adult women anywhere in the world.

The 1993 National Immunisation Strategy repaired more than a decade of neglect and complacency, fragmentation and absence of national leadership. Previously, states and territories used different vaccine schedules, vaccine pricing varied nationally, and pertussis and measles in particular were not well controlled. For measles, there was an average of 2,418 cases and 517 hospitalisations per year, with seven deaths, during 1993-97.

Three waves of policy changes, backed by high level political support, built a sophistication and integrated national system across Australia’s three levels of government.

**Wave 1**: The National Strategy included clear responsibilities for immunisation through a National Childhood Immunisation Agreement between the Commonwealth and the states/territories, better mechanisms for recording and reporting immunisation coverage, and better co-ordination between public and private sector providers. It also recommended targets for immunisation coverage.

The groundbreaking population-based Australian Childhood Immunisation Register (ACIR) followed in 1996. This is based on enrolment in Australia’s universal health care coverage system, Medicare. It enabled detailed geographical tracking of coverage, reminders for overdue immunisation and consolidated immunisation histories for parents and providers.

**Wave 2**: In 1997, the then Minister for Health Michael Wooldridge launched the Immunise Australia program. Its ‘Seven Point Plan’ comprised:

- initiatives for parents, such as a maternity immunisation allowance and child care benefits for fully immunised children;
- a greater role for general practitioners, including incentives such as a service payment for each immunisation encounter, and outcome incentives based on practice-based coverage calculations;
- monitoring and evaluation of immunisation targets through the ACIR;
- immunisation days;
- primary-school-based MMR immunisation in an effort to eliminate measles;
- education and research, including community education, and the creation of the National Centre for Immunisation Research and Surveillance (NCIRS) at the University of Sydney with funds from the Australian Government; and
- school entry immunisation requirements.

Prior to 1997, an expert subcommittee of the National Health and...
Medical Research Council produced national clinical guidelines on immunisation for health professionals. These guidelines were, however, not directly related to government vaccine funding decisions. In 1997, the Australian Technical Advisory Group on Immunisation (ATAGI) was established, providing advice directly to the federal health minister. The National Immunisation Committee (including all state and territory immunisation co-ordinators and representatives of private providers) was established to ensure that implementation issues were addressed in a co-ordinated manner.

**Wave 3:** In the mid 2000s, Australian Immunisation Agreements enhanced co-ordination between Commonwealth and state/territory governments, leading to consistent funding of all vaccines on the National Immunisation Program (NIP), in return for agreed outcomes for immunisation coverage and vaccine wastage. All states developed robust mechanisms for quality-controlled vaccine delivery to immunisation providers, and implemented school-based immunisation programs. NCIRS received additional funding, more appropriate to the detailed technical support required by ATAGI and the NIP.

In 2005, federal legislation aligned vaccine funding applications with the established, transparent and predictable framework for new medications, through the Pharmaceutical Benefits Advisory Committee (PBAC). The Australian Pharmaceutical Benefits Scheme uses a standardised cost-effectiveness evaluation based on price per disability- or quality-adjusted lifetime saved for decision-making. The PBAC process has supported the introduction and public funding of new vaccines, including rotavirus and HPV vaccines.

Since the inception of the ACIR, immunisation coverage has steadily increased, with full immunisation coverage for core NIP vaccines rising from 75% in 1997 at 12 months of age, and 83% of 24-month-olds receiving one dose of MMR vaccine, to 91.4% fully immunised at 12 months and 92.5% at 24 months by 2010.

Two further Australian capabilities contribute to global immunisation. The Australian national regulatory authority (NRA) for medicines and therapeutic devices, the Therapeutic Goods Administration (TGA), is a leading authority in the Asia-Pacific region, hosting two WHO Collaborating Centres, including one dedicated to quality assurance of vaccines and other biologicals. The TGA works with WHO to help strengthen the capacity of NRAs in the region to license new products, regulate vaccines and medicines, and monitor their safety.

Additionally, Australia’s network of researchers supports clinical trials, training in Good Clinical Practice and other regulatory requirements for a wide range of globally relevant vaccines for children, adolescents and adults. These research centres support collaborations in countries such as Indonesia (e.g. Murdoch Childrens Research Institute/Royal Children’s Hospital Melbourne); PNG (e.g. Telethon Institute for Child Health Research); Fiji (Centre for International Child Health, Royal Children’s Hospital Melbourne); and Vietnam (e.g. Menzies School of Health Research).

**Australian Government development assistance**

Australian official development assistance (ODA) for health has increased substantially, from US$27.85 million in 1990 to AUS$385 million in 2007-08 and AUS$420 million in 2008-09.

In 2011/12, expenditures on health are projected to be AUS$759 million. In 2012, the Australian government kept ODA at the same level in real terms, at 0.35% of Gross National Income (GNI), breaking its commitment to increase Official Development Assistance (ODA) to 0.38%, towards a goal of 0.5% in 2015-6 – still considerably below the UN target of 0.7%. Australia’s ODA ranks in 13th place among the 23 OECD donor countries, and well below the OECD average of 0.46% GNI.

Between its establishment in 2000 and 2011, GAVI has received over US$4 billion in direct donor contributions, as well as long-term contributions and commitments of US$6.27 billion and US$1.5 billion for its International Finance Facility for Immunisation (IFFIm) and Advanced Market Commitment (AMC), respectively. Between 2006 and 2010, Australia provided a total of AUS$34 million in core funding to GAVI. In March 2011, Australia signed an agreement for a contribution of AUS$250 million over 20 years to the IFFIm – AUS$12.5 million per year on average. For 2011-13, Australia committed AUS$20 million per year for core GAVI funding, and this was increased in June 2011 at GAVI’s pledging conference where Australia committed to invest an additional A$140 million between 2011 and 2013.

The proportion of Australia’s development assistance for health that targets immunisation is difficult to ascertain, as it takes various forms including support for health systems strengthening or broader child health services, rather than specific immunisation programs. An example of the impact of a relatively modest Australian investment is shown for hepatitis B (Box 1). The implementation of priority interventions, operational evaluation addressing important program issues, and engagement with policymakers enabled earlier adoption and transition to full country support. This contrasts with Hib vaccine, which none of the independent Pacific island countries introduced without initial donor support, and in the absence of co-ordinated support, implementation has been piecemeal and slow. Only in 2011 did Vanuatu introduce Hib vaccination, the last Pacific island country to do so.

**Future opportunities for Australia**

A comprehensive approach to immunisation could have three core components: to develop new vaccines; to deliver currently available vaccines to those who need them; and to sustain programs as essential health system platforms. Each component would be underpinned by deliberate advocacy for engagement by other donors and government and civil society partners.

**Develop** – The Australian government can prioritise funding through its national research council and AusAID for basic and clinical research into vaccines for unmet medical needs in the poorest countries. Australian institutions and international partnerships, including public-private partnerships such as the International AIDS Vaccine Initiative, the Malaria Vaccine Initiative, the International Vaccine Institute, and the Aeras Global TB Vaccine Foundation can be considered. Research priorities can reflect global and regional need, including falciparum malaria resistant to artemisinin-based combination therapies, vivax malaria, dengue, TB, HIV and hepatitis C, as well as non-target disease-specific vaccine effects. Australia can also support technical and regulatory
assistance for local vaccine manufacture, emphasising quality control processes, including WHO prequalification. SARS and recent influenza illustrate the compelling rationale to strengthen outbreak surveillance systems for emerging infections including zoonoses, and for the evaluation of new vaccines and established vaccines in developing country contexts. For example, Australia could support increasing access to influenza vaccines in developing countries, including for children.

**Deliver** – In keeping with MDG commitments and the health gains they represent beyond 2015, Australia has an opportunity to increase its efforts to promote vaccine access, using a range of channels, including the GAVI Alliance and Australia’s regional and bilateral aid programs. Through its knowledge hubs and programming, AusAID is already deepening its expertise in health

**Box 1: Support for hepatitis B immunisation in the Asia-Pacific region.**

The Lombok Hepatitis B Model Immunisation Project (1987-91) in Indonesia was the first model program sponsored by the International Task Force on Hepatitis B Immunisation, with initial funding from the James S. McDonnell Foundation and later the Australian Government. The project aimed to incorporate HB immunisation into the routine immunisation program, with a birth dose to prevent the 25% of chronic HB infections acquired through mother-to-infant transmission. As 94% of births occurred at home, 88% with a traditional rather than a professional birth attendant, community-based notification that enabled health workers to visit and immunise newborns at home soon after birth was required. The project achieved more than 90% coverage with 3 vaccine doses and substantially reduced HB infection; the rate of infection was halved for children who received the first vaccine dose within 7 days of birth. Coverage of other vaccines increased. While a national commitment to progressively introduce universal infant HB immunisation followed, home visits for HB birth dose immunisation were felt too resource intensive. Further field evaluations integrated a HB birth dose with an essential package for mothers and newborns, today’s global standard of care.

A distinctive pre-filled, non-reusable, compact, easy-to-use injection device (UnijectTM) was shown to be effective for midwives to deliver the HB vaccine birth dose to newborns at home, beyond the reach of the vaccine cold chain, thanks to the vaccine’s heat stability. This work demonstrated how immunisation programs can strengthen the primary health care system. Beyond the implementation of universal HB vaccination, it encouraged Indonesian policy development for home visits by health staff to deliver a package of essential maternal and newborn care in the first week and first month of life, and a national program to provide a midwife in every village.

Australian support also played a decisive role in HB control in Pacific Island Countries (PICs), where infection rates were among the world’s highest. While many PICs adopted HB immunisation by the early 1990s, vaccine supply was uncoordinated, erratic and often insufficient. From 1995, the Control of Hepatitis B Infection in PICs Project improved vaccine supply utilising the established regional UNICEF vaccine procurement mechanism and donor-capitalised revolving fund. Country financing successfully replaced donor funding. The project reinvigorated regional technical and training support for country immunisation program staff, and coordination through UNICEF and WHO.

Support is needed, not only for timely and equitable access for those with greatest need for new vaccines like pneumococcal conjugates, rotavirus and HPV, but also for wider and more effective use of underused vaccines like rubella and influenza. Piggy-backing elimination of foetal damage due to rubella onto already highly effective programs to eliminate measles is ‘low hanging fruit’, as would be using the introduction of pneumococcal and rotavirus vaccines to strengthen treatment programs for diarrhoea and pneumonia.

Australia could pursue other innovative approaches, targeting countries that are or soon will be too wealthy for GAVI support but have suboptimal immunisation programs. There are regional opportunities to accelerate the use of new and underused vaccines through a revolving fund and pooled procurement (as in the Americas, and as has been discussed in WHO’s EMRO region). This could create opportunities for smaller countries to increase their purchasing power and gain greater access to tiered pricing. Additionally, as countries strengthen their immunisation programs, there is on-going need for operational and policy research to evolve better capacity and practices of financing, monitoring and evaluation, and ensuring uptake. This would need to be coupled with continuous efforts to build local capacity for innovation, implementation and evaluation.

**Sustain** – The Asia-Pacific region trails the Americas in political commitment to immunisation. Australia could contribute to a fundamental shift here, one essential for the long-term achievement of the promise of immunisation. Australian advocacy could help develop political support for immunisation, and its translation into long-term, predictable financing. Options here include a greater role for the Asia Development Bank to support national immunisation funding schemes, engaging Australia’s thriving retail and institutional banking sectors for a private float to support the International Financing Facility for Immunization (IFFIm), and promoting an immunisation agenda in key political fora, such as Asia-Pacific Economic Collaboration (APEC).

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**Competing interests**

TN chairs the Australian Government’s Technical Advisory Group on Immunisation (ATAGI). KT was formerly Vice-President, Global Vaccine Policy and Public Health Partnerships; and TR formerly Clinical R&D and Medical Affairs Director, Australia-New Zealand-Oceania (1998-2003) in GlaxoSmithKline Biologicals.
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Invited Commentary

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Australia, immunisation, GAVI, and the non-specific effects of vaccines

Professor Frank Shann
Royal Children’s Hospital, Victoria

In this issue, Ruff, Taylor and Nolan draw attention to the important role that Australia could play in improving global health through immunisation. As they point out, Australia has made major contributions to vaccine science, and could substantially reduce child mortality by contributing extra money and expertise to the Global Alliance for Vaccines and Immunisation (GAVI). The Expanded Programme on Immunization (EPI) provides a minimum immunisation schedule for children in developing countries, where 98.7% of child deaths occur.¹ The current EPI schedule is for BCG and polo vaccine at birth; whole-cell diphtheria-pertussis-tetanus vaccine (DPT) and polo vaccine at 6, 10 and 14 weeks of age; measles vaccine at 9 months; and DPT booster at 18 months. This protects against disseminated tuberculosis, polio, diphtheria, pertussis, tetanus and measles; but, unfortunately, these are not the main causes of child mortality, even in unvaccinated communities.² The main killers are pneumonia, sepsis and diarrhoea.
so we should be providing conjugate pneumococcal vaccine and rotavirus vaccine, and developing vaccines that protect against non-serotypeable *Haemophilus influenzae* as well as all serotypes (not just type b). GAVI is attempting to provide universal access to many of these more expensive vaccines, and Australia should enthusiastically support this initiative.

There is another dimension of global immunisation to which Australia could make a substantial contribution. There is exciting evidence that the EPI vaccines have very substantial non-specific (heterologous) effects in children in high-mortality countries. Until the next vaccine is given, BCG vaccine approximately halves mortality from infections other than tuberculosis and, providing vitamin A has not been given at birth, measles vaccine approximately halves mortality from infections other than measles. Conversely, until the next vaccine is given, DPT increases mortality in girls from infections other than diphtheria, tetanus and pertussis. In general, live vaccines reduce mortality from non-target infections, while inactivated vaccines increase mortality from non-target infections (Table 1).

We can no longer assume that a vaccine acts independently from other vaccines or that it influences only infections caused by its target disease. This has profound implications for vaccine policy. The EPI vaccines do not target the major causes of death, and the main reason the EPI saves lives is probably because BCG and measles vaccine reduce mortality from pneumonia and sepsis – which are the main causes of death. We could save many more lives by making better use of the beneficial non-specific effects of BCG and measles vaccine. So far, most of the research has been done by a Danish group working in Guinea-Bissau, in West Africa, and we urgently need randomised trials to test the non-specific effects of the EPI vaccines outside West Africa. This is precisely the type of research that could be supported by Australia; such trials are difficult to perform, but we have both the expertise and the money to support them in high-mortality communities in our region.

In randomised trials, BCG reduced mortality from diseases other than tuberculosis by 25% (95% CI 6-64%) in children in the USA and UK in 1948-61, by 64% (1-87%) when given at 19 months of age in Guinea-Bissau, and by 48% (18-67%) in the first four weeks of life when given to low-birthweight babies in Guinea-Bissau. Despite the evidence that BCG halves neonatal mortality, less than 50% of infants are given BCG during the neonatal period in high-mortality countries. BCG is usually supplied in 10-dose or 20-dose vials, and many health clinics delay opening a vial until they have a large number of infants to vaccinate – missing a golden opportunity to reduce mortality. We should either supply small clinics with single-dose syringes of BCG, or say that BCG from a multi-dose vial should be given even if it is needed by only one child.

In randomised trials, providing it was not given after neonatal vitamin A or followed by DPT, BCG vaccine approximately halves mortality from causes other than measles by 47% (23-63%) when given to girls aged 9-10 months in Guinea-Bissau, Senegal, and Sudan, and by 35% (95% CI 1-57%) when given at 4.5 months of age in Guinea-Bissau (rows 4-5 in Table 1). Radical changes in policy should follow from the fact that measles vaccine reduces mortality from pneumonia and sepsis, as well as measles. At present, measles vaccine is given at 9 months of age in high-mortality countries; if it is given later, many children die from measles before they are immunised; if it is given earlier, the antibody response is impaired because of the effects of maternal antibody. This policy completely ignores the beneficial non-specific effects that occur when measles vaccine is given in early infancy, and it assumes that mortality from measles is determined by measles antibodies. In fact, fatal measles infections occur in individuals with defective cellular immunity but not in individuals with agammaglobulinaemia, yet we base our measles immunisation policy around antibody levels (largely because they are easier to measure, but also because high levels reduce the spread of measles). Policy-makers should clearly distinguish between total lives saved, lives saved from measles, non-fatal cases of measles, and antibody levels.

If an extra dose of measles vaccine is given at 18 weeks, at least 4 weeks after the last dose of the primary course of DPT, we get good protection against death from measles as well as a substantial reduction in mortality from pneumonia and sepsis; and the effect on pneumonia and sepsis is much greater if the child still has maternal antibody at the time of measles immunisation. This effect is so important that it suggests that it may be preferable to give only two doses of DPT in infancy, at 6 and 10 weeks, so that the extra dose of measles vaccine could be given at 14 rather than 18 weeks, in addition to the usual dose at 9 months. To reduce the adverse effects of DPT, a third dose of measles vaccine (or a second dose of BCG) should be given at 19 months, at least 4 weeks after the 18 month booster dose of DPT.

In contrast to BCG and measles vaccine, DPT may *increase* mortality from pneumonia, sepsis and diarrhoea (Table 1, rows 6-8). In the only large study of the introduction of DPT into a high-mortality area, mortality was 1.9-fold (1.2-3.5) higher among children who received DPT in Guinea-Bissau. In the randomised trial of BCG at 19 months in Guinea-Bissau, mortality was 5.1-fold (2.0-16.7) higher with BCG-then-DPT compared to DPT-then-BCG. In the randomised trial of BCG in neonates in Guinea-Bissau, mortality approximately halves mortality from infections other than diphtheria, tetanus and pertussis. In general, live vaccines reduce mortality from non-target infections, while inactivated vaccines increase mortality from non-target infections (Table 1).

In randomised trials, providing it was not given after neonatal vitamin A or followed by DPT, BCG vaccine approximately halves mortality from causes other than measles by 47% (23-63%) when given to girls aged 9-10 months in Guinea-Bissau, Senegal, and Sudan, and by 35% (95% CI 1-57%) when given at 4.5 months of age in Guinea-Bissau (rows 4-5 in Table 1).

### Table 1: The main studies of the non-specific effects of the Expanded Programme of Immunization (EPI) vaccines on all-cause mortality in high-mortality countries (adapted from reference 6).

<table>
<thead>
<tr>
<th>BCG (randomised trials)</th>
<th>Mortality rate ratio (95% CI)</th>
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<tbody>
<tr>
<td>1. USA and UK, 1948-61: 0-21 yr.</td>
<td>0.75 (0.59-0.94)</td>
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<tr>
<td>2. GB, after DPT-booster: 19 mo to 60 mo.</td>
<td>0.36 (0.13-0.99)</td>
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<tr>
<td>3. GB, low-birth-weight neonates: birth to 4 wk</td>
<td>0.52 (0.33-0.82)</td>
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<tr>
<td>Measles vaccine (randomised trials)</td>
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<tr>
<td>4. Gambia, GB, Senegal, Sudan: girls, 10 to 36-60 mo.</td>
<td>0.53 (0.37-0.77)</td>
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<tr>
<td>5. GB, no vitamin A and after DPT3: 4.5 to 36 mo.</td>
<td>0.65 (0.43-0.99)</td>
</tr>
<tr>
<td>DPT (not randomised)</td>
<td></td>
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<tr>
<td>6. First use in GB: for 6mo after immunisation clinic</td>
<td>1.92 (1.04-3.52)</td>
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<td>7. GB, BCG-then-DPT v DPT-then-BCG, 19 to 60 mo.</td>
<td>5.12 (2.01-16.7)</td>
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<td>8. GB, BCG at birth: DPT by 2 mo of age, 2 to 6 mo.</td>
<td>4.33 (1.54-12.2)*</td>
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<td>*Subgroup analysis within a randomised controlled trial; bias very unlikely.</td>
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<td>GB: Guinea-Bissau; UK: United Kingdom; USA: United States of America.</td>
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mortality in the BCG group was 4.3-fold (1.5-12.2) higher among children who had received DPT by 2 months of age. The increased mortality when DPT was the most recent vaccine is unlikely to be explained by confounding in these studies. Because pneumonia and sepsis cause many more deaths than diphtheria, pertussis and tetanus, even a small increase in mortality from pneumonia and sepsis would offset the lives saved by the effect of DPT on its target diseases.

A key determinant of child mortality is the most recent vaccine administered; BCG and measles vaccines reduce mortality, but DPT increases mortality. With the current EPI schedule, which includes a booster dose of DPT in the second year of life, DPT is the most recent vaccine for 50 of the 60 months between birth and 60 months. DPT would be the most recent vaccine for only 3 of the 60 months if the schedule were changed to BCG-polio at birth, DPT-polio at 6 and 10 weeks, measles vaccine at 14 weeks and 9 months, DPT booster at 18 months, and measles vaccine at 19 months. If all neonates were given BCG at birth and this new immunisation schedule were adopted, under 5 mortality would probably drop by at least 30%, or 2-3 million deaths a year. This huge reduction in mortality would be achieved at very low cost, using only vaccines that are already in the routine EPI schedule.

There are several other important implications of the non-specific effects of vaccines. First, we can no longer assume that the benefits of a vaccine are in direct proportion to its effect on the target disease. For example, if pertussis causes 400,000 deaths a year, we cannot assume that universal use of a whole-cell vaccine with 85% efficacy would reduce child mortality by 340,000 (400,000 x 0.85) deaths a year – it might increase mortality from pneumonia and sepsis. Second, we need to be careful about using ‘vaccine probe’ studies of the cause of death. For example, the observation that pneumococcal conjugate vaccine reduced mortality by 16% in The Gambia does not necessarily mean that the serotypes of pneumococcus in the vaccine caused 16% of child deaths; the vaccine may have reduced mortality from pneumococcal infection by more than 16%, with the additional lives saved being offset by harmful non-specific effects of the vaccine. Conversely, pneumococci may have caused less than 16% of deaths if the vaccine had beneficial non-specific effects. Third, DPT should not be given after measles vaccine (for example, in catch-up campaigns). Fourth, DPT3 (which has harmful non-specific effects) should not be used as the main measure of full EPI coverage; rather, we should use the proportion of children who receive all the scheduled doses of measles vaccine (which has beneficial non-specific effects) by 24 months of age. At present, there is no incentive for measles vaccine to be given after 12 months of age because these doses are not counted, and more emphasis is given to DPT3 than measles vaccine.

Australia is in a position to make an important contribution to immunisation in high-mortality countries by supporting the far-sighted initiatives being made by GAVI to improve the range of vaccines given to children, and by fostering research into the non-specific effects of vaccines. A relatively modest contribution by Australia could have truly spectacular effects on global health.

References

Correspondence to: Professor Frank Shann, ICU, Royal Children’s Hospital, 50 Flemington Road, Parkville Victoria 3052; e-mail: shannf@netspace.net.au