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Introducing New Vaccines into the South African National Immunisation Programme - A Case Study

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Guest editorial

Introducing new vaccines into the South African national immunisation programme – A case study

Over three decades ago the mother of all public health declarations, the 1978 WHO and UNICEF sponsored Alma Ata Conference, set its goal of achieving ‘Health for All’ by the year 2000. Much has been achieved since then with vaccines playing a major role in controlling infectious diseases throughout the world. However, much still remains to be achieved. For example, poliomyelitis remains to be eradicated over a decade past the original target date of 2000 and measles, once also targeted for eradication, is still responsible for 1% of all child deaths worldwide [1]. Several global health initiatives have been established to promote immunisation within the context of the other primary healthcare interventions. The Global Immunisation Vision and Strategy (GIVS) was established in 2005 with the specific aim of reducing vaccine-preventable diseases mortality and morbidity by 2/3 by 2015 as compared to 2000 [2] and the Global Alliance for Vaccines and Immunisation (GAVI) was established in 2000 to provide financial support for immunisation to the poorest countries of the world [3]. Unfortunately, the toll from infectious diseases, much of which is vaccine-preventable, remains depressingly high. It has been estimated that in 2008 some 68% (5.970 million) of the 8.795 million deaths worldwide in children less than 5 years of age was due to infectious diseases [1], with sub-Saharan Africa bearing a major portion of this toll [4]. Of concern is that inadequate access to vaccines is responsible for over 2 million deaths annually in low and middle income countries [5]. It is clear that much ground needs to be made up, in particular in the immunisation field, in order to meet Millennium Development Goal 4 to reduce the under-five mortality rate by 2/3 by 2015 from the 1990 figure.

The Expanded Programme on Immunisation (EPI) was established in 1974 by the WHO on request from the World Health Assembly (WHA) in order to provide a set of life-saving vaccines to the children of the world [6]. In 2008, 106 million children were immunised against the standard six vaccine-preventable infectious diseases – TB, diphtheria, whooping cough, tetanus, polio and measles [7], and South Africa was no exception. The hepatitis B vaccine was added to the South African EPI schedule in 1995, in line with the recommendations by the WHA and WHO. By 2008, it was shown that the great majority of the infectious diseases burden in the world lay outside of these diseases. Globally, nearly half of all deaths in children under 5 years of age were due to pneumonia (18%), diarrhoea (15%) and meningitis (2%) much of which is preventable by three new vaccines – pneumococcal conjugate vaccine (PCV), rotavirus vaccine and the Haemophilus influenzae type b (Hib) vaccine. However, new vaccines are costly and well beyond the financial means of countries in the developing world where these diseases are most problematic. South Africa, classified by the World Bank as an upper middle income country [8] became the first country in sub-Saharan Africa to introduce all three new vaccines into its routine immunisation schedule, Hib in 1999, and PCV and rotavirus a decade later in 2009. In addition a new pentavalent vaccine containing inactivated polio vaccine (IPV) was introduced into the routine schedule in 2009. This supplement tells the story behind introduction of these new vaccines in South Africa.

Introducing new vaccines into a country’s immunisation schedule is by no means a simple exercise, particularly outside of the developed world, and a comprehensive document issued by WHO details the myriad of policy and programmatic issues which need to be evaluated before making this weighty decision [9]. Amongst these are the disease burden in the country, the efficacy of the vaccine, financial sustainability, public perceptions and community pressures especially equity issues in a heterogeneous population as well as programmatic impacts including human resources availability and programme sustainability. As a country South Africa is a paradigm of many of these sometimes conflicting issues which face countries outside of the industrialised world. On the one hand South Africa has fallen short of its EPI targets and, in fact, UNICEF has even suggested that immunisation rates may well have fallen since 1994 [10]. Yet, on the other hand, the well-resourced private health sector of the country, comprising about 15% of the population who are on a medical insurance scheme, have received all the new vaccines which are part and parcel of the immunisation schedules of the developed world underlining the severe equity pressures in the country. In addition, although the country’s health budget is the largest on the continent, its National Department of Health has to contend with massive conflicting health priorities such as the world’s largest number of people living with HIV with the world’s largest antiretroviral treatment programme further aggravated by a huge TB burden, one of the largest in the world.

This supplement is particularly timely given the number of new vaccines being introduced into the developed world and the complexity of the challenges faced by the developing world who are the major victims of these vaccine-preventable diseases. Much can be learned from the South African experience. The supplement covers nearly every aspect of the spectrum of issues which needed to be evaluated before the Minister of Health could make the final decision. The decision-making process is dealt with from a WHO, an African and a national South African perspective [11,12]. The early successes which followed the introduction of PCV [13] and rotavirus [14] vaccines are of great interest given the relatively low coverage achieved so far for these vaccines and the
superimposed spectre of HIV. The addition of a pentavalent (DTaP-IPV/Hib) vaccine to the routine schedule at the same time brought a new dimension to considerations of polio control on the continent which, in 2012, appears to be the main last bastion of the infection [15]. The pentavalent vaccine made South Africa the first country on the continent to introduce IPV. Follow-up surveillance of Hib, introduced in 1999, has now highlighted significant deficiencies in the control of the infection which needs to be addressed [16] while the hepatitis B vaccine immunisation programme, initiated in 1995, has been far more successful [17]. The merits and obstacles for a future introduction of a costly (HPV) vaccine [18] as well as a cheap (rubella) vaccine [19] are analysed. The very important consideration of the influence of HIV infection on vaccine policies is of special concern in a country like South Africa but also in many developing countries [20]. The programmatic and logistical advantages of combination vaccines are discussed in the South African setting [21]. The supplement is then followed by the programmatic issues of social mobilisation, advocacy and education in the context of new vaccines introduction for the general public [22] as well as for healthcare workers [23]. Lastly, the all-important issue of making provision for sustainable financing in the face of mammoth competing health priorities concludes the supplement [24].

References


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Review

New vaccine introduction in the East and Southern African sub-region of the WHO African region in the context of GIVS and MDGs

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Abstract

Immunization programmes have over the years proven to be effective and useful in infectious disease control. However, based on current trends that show that many developing countries will not reach the Millennium Development Goals (MDG) targets, there is an urgent need to accelerate efforts to control the most common conditions still responsible for the largest morbidity and mortality in children under 5 years of age, like diarrhoea and pneumonia, for which safe and effective vaccines are now available.

Through World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) strategies and initiatives like the Global Immunization Vision and Strategy (GIVS), Accelerated Disease Control and Reach Every District (RED), major positive achievements like the increasing number of children reached with Diphtheria–Tetanus–Pertussis (DTP) vaccines, significant measles mortality reduction, and the almost complete eradication of polio, have been realised. Many children in developing countries have access to life saving vaccines through the Global Alliance for Vaccines and Immunization (GAVI) support. Supplementary immunization activities against measles and polio continue to offer opportunities to deliver measles and polio vaccines, and other life-saving interventions.

The Global Immunization Vision and Strategy 2006–2015 (GIVS framework) can effectively be used to guide countries in addressing some of the remaining challenges to reach the unreached and increase coverage of traditional vaccines, immunize more people against more diseases, support decision making to introduce new vaccines, as well as recognize the opportunity to invest in community health through cost-effective immunization programmes. Introduction of new vaccines should be strengthened and used as vehicles for health systems strengthening as well as for delivery of comprehensive primary health interventions to impact positively on the spiralling disease burden and reduce overall child mortality. A number of countries have adopted and operationalized GIVS through comprehensive multi-year plans for immunization (cMYP).

This paper reviews progress with respect to introduction of some of the new vaccines in the East and Southern sub-region of WHO African region in the context of GIVS and MDGs as well as the challenges thereof.

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1. Introduction

It was at the World Health Assembly (WHA 27.57) in 1974 that a recommendation was adopted to establish the Expanded Programme on Immunization (EPI). The EPI has since been reported to have reached 82% of children with three doses of Diphtheria–Pertussis–Tetanus (DTP) by 2009 [1]. EPI was established and built on the basis of the successful global smallpox eradication in 1977. Its aim was to ensure that all children worldwide benefit from relatively affordable, life saving vaccines [1]. Immunization has not only helped eradicate smallpox, but also reduced the burden of polio by 99% globally, reduced measles deaths by 89% in the World Health Organization’s (WHO) African region by 2009, and is reported to avert 2.5 million deaths annually. EPI has also played a considerable role as a health system strengthening pillar through which other proven life saving interventions have been delivered to communities [1].

In its original stages, EPI was designed to deliver six traditional vaccines against diphtheria, pertussis, tetanus, polio, measles and tuberculosis. This programme was considered as one of the fundamental elements of the WHO strategy to achieve health for all by 2000. To date, most countries, including the majority of low income countries have introduced hepatitis B (Hep B) and Haemophilus influenzae type b (Hib) (currently referred to as under-utilised
vaccines) while an increasing number are in the process of adding the pneumococcal conjugate and the rotavirus vaccines (i.e., new vaccines) [1]. By the end of 2010, all 19 countries in the East and Southern Africa (ESA) sub-region of the African region of WHO, had introduced the Hep B and Hib vaccines to their routine childhood immunization schedules.

1.1. Immunization in the context of Millennium Development Goals (MDG’s)

Affiliated countries signed the United Nations Millennium Declaration of the United Nations in September 2000, where goals were set for countries to support reduction of poverty and improve human development. Millennium Development Goal number four (MDG 4) aims to reduce by two thirds, mortality rates amongst children under five years (USMR) by 2015 compared to 1990 [2]. This commitment was reaffirmed at the UN General Assembly Special Session on Children, calling for intensification of tested, cost-effective interventions against diseases and malnutrition [3].

Most of the efforts to meet the MDG 4 have concentrated in developing countries which account for 90% of USMR [2]. Increasing immunization coverage, especially with new vaccines, came into the spotlight as one of the driving forces that can significantly assist the efforts to meet this goal.

According to the United Nations MDG monitor, with less than 5 years to the set target by 2015, many countries have made tremendous gains in health related targets [2]. Most countries in Africa are however off track to achieve the MDG’s for maternal and child mortality reduction. It is also unfortunate that most countries not likely to meet the set targets are currently plagued by HIV/AIDS, conflict and economic hardships [2,4].

Sub-Saharan Africa accounts for 11% of the total population of the world, and is accountable for half of all maternal and child deaths in the world [6] (Table 1; Fig. 1). In addition, all but one of the thirty-one countries with the highest USMR, except Afghanistan are in Sub-Saharan Africa [5]. Sub-Saharan Africa unfortunately also bears the largest burden of maternal mortality in the world [6].

It is important to note that while significant strides have been made towards reducing child deaths, there is still a lot that needs to be done. The United Nations MDG monitor reports that a child born in a developing country is 13 times more likely to die before reaching the age of five compared to a child born in an industrialized country [2]. Vaccine preventable diseases are unfortunately still responsible for 25% of child deaths. This is mainly due to unavailability of vaccines against pneumonia and diarrhoea. Thus, vaccines have a significant contribution to play in achieving MDG 4, by offering additional prevention against diarrhoea and pneumonia which account for almost a third of all child deaths [7].

1.2. Immunization in the context of Global Immunization Vision and Strategy (GIVS) 2006–2015

The 58th WHA (WHA 58.15) in 2005 recognized the role vaccination can play to meet the MDG’s and urged all countries to adopt the WHO/UNICEF GIVS as a framework to strengthen immunization programmes between 2006 and 2015. This strategy aims at protecting more people with immunization beyond infancy in an environment where immunization is highly valued and all people have access to life saving vaccines. The GIVS aims not only to sustain high immunization coverage with the traditional vaccines but also emphasizes the need to reach the unreached, extend vaccines beyond infancy, encourages and anticipates introduction of new vaccines and technologies for all, encourages packaging of life saving interventions to reduce mortality, as well as financial sustainability of immunization programmes.

This strategy was developed in order to use this proven public health intervention to reduce child mortality and disease burden, in an environment where there is increased demand for immunization, there are numerous new vaccines against more infectious diseases, there are more threats for pandemics as well as opportunities for global partnerships to strengthen health systems [9]. In order to guide implementation of national immunization programmes, analyse costs and finances, and plan for financing and financial sustainability of immunization programmes, WHO and UNICEF have supported countries to develop comprehensive multiyear plans (cMYP) for immunization in line with GIVS. The development of cMYP’s presents an opportunity to link immunization with other interventions, strengthen health systems and therefore reduce child and maternal mortality [10].

2. Status of introduction

The state of the world’s vaccines and immunization report of 2009 attributes the slow progress in introduction of under-utilised and new vaccines to amongst others the underlying health system weaknesses in developing countries, the difficulty in delivering new interventions through already overloaded logistical systems and infrastructures as well as the lack of understanding of the value of vaccines especially in the poorest population [8].

Global Alliance for Vaccines and Immunization (GAVI) has greatly supported delivery of vaccines in 13 low income countries out of the nineteen (19) countries in the East and Southern African countries of the AFRO region. Botswana, Lesotho, Mauritius and Namibia, classified as low middle income states, and South Africa being an upper middle income country, are the five countries in the sub-region that are ineligible for GAVI support to procure and deliver vaccines.

In the first phase of support between the years 2000 and 2005, GAVI concentrated on supporting countries to introduce hepatitis B, Hib and yellow fever vaccines. GAVI has in the second phase
which started in 2006 until 2015 [8], expanded its support to the introduction of pneumococcal and rotavirus vaccines. The Alliance furthermore introduced a co-financing system where countries are expected to gradually take over the financing of immunization systems.

2.1. Hepatitis B vaccine

WHO classifies hepatitis B as a major public health problem and estimates that nearly 30% of the global population have serological evidence of hepatitis B virus infection and that 350 million of these people live with chronic HBV infection, with a million of them dying annually from chronic liver disease, including cirrhosis and liver cancer. Nonetheless, there is a safe and effective vaccine against hepatitis B since 1982. WHO has therefore recommended the inclusion of the hepatitis B vaccine in childhood routine immunization in all countries [11].

2.1.1. WHO AFRO region

It is estimated that 18.5 million people in the WHO AFRO region are infected with hepatitis B, with 2,915,000 chronic infections and 276,000 deaths [12]. Hep B is one of the under-utilised vaccines that experienced very slow progress in introduction to EPI in most developing countries, partly due to funding constraints. However, 45 of the 46 countries in the region had introduced Hep B vaccine at the end of 2010 [12,13]. In East and Southern Africa, the last country introduced Hep B in September 2009 [15]. AFRO proposed a disease control goal to include, inter alia, a birth dose in all countries as recommended by the Strategic Advisory Group of Experts (SAGE) in 2009 [14].

2.2. H. influenzae type b

The introduction of Hib vaccine has improved following initial delays, since the recommendation by WHO and endorsed by SAGE through the WHO position paper in November 2006, urging countries to introduce Hib vaccines into national immunization programmes. It is however still disturbing that only 48% of the 2009 global birth cohort lived in countries where these vaccines are available because countries with larger populations like China, India, Indonesia and Nigeria are still to introduce Hib vaccines into their national immunization programmes [16].

2.2.1. WHO AFRO region

44 out of the 46 countries in AFRO had introduced Hib vaccine at the end of 2010 with Nigeria having made an application to GAVI for introduction of Hib containing pentavalent vaccine [17].

2.2.2. East and Southern (ESA) sub-region

By the end of 2010, all nineteen ESA countries of WHO AFRO, had successfully introduced vaccines against Hib. The last two countries to introduce Hib vaccine were Seychelles and Botswana in November 2010 [18].

2.3. Pneumococcal conjugate vaccines

Pneumococcal infections cause many deaths in developing countries [19,20], the bulk of which lie in HIV infected individuals; a further problem is the rising resistance to antibiotics. The WHO made a recommendation in March 2007 to introduce pneumococcal conjugate vaccines (PCV) to national immunization as a strategy for control of pneumococcal diseases [20,21]. The introduction of PCV was also emphasized for countries with child mortality rates above 50/1000 live births as well as countries with high HIV burden.

Initially, in 2007, when the recommendation to introduce PCV was made, only the 7-valent vaccine (PCV-7) was available to use as a safe and effective vaccine. Given the considerable public health impact of successful introduction of PCV, WHO emphasized the need to prioritize development of safe, effective and affordable vaccines, offering broader protection against pneumococcal diseases...
[20]. This has led to subsequent availability of the 10-valent (PCV-10) and 13-valent (PCV-13) vaccines.

2.3.1. WHO AFRO region

In WHO AFRO, 7 out of the 46 countries had introduced PCV by the end of 2010. An additional 17 countries have however successfully applied for GAVI Support to introduce PCV to their routine schedule. The countries in West Africa that have made applications are: Ghana, Guinea Bissau, Guinea, Nigeria, Niger, Liberia, Mauritania, Togo and Senegal; while the countries in Central Africa are: Angola and Sao Tome and Principe; as well as a further 3 countries in the ESA sub-region [17].

2.3.2. ESA sub-region

By the end of 2010, 2 countries (South Africa and Rwanda) had introduced PCV-7 among the 19 countries in the sub-region [18]. Rwanda was supported by GAVI, while South Africa self-financed the introduction of PCV-7. This was followed by availability of PCV-10 and PCV-13 globally. This has led Kenya to introduce PCV-10 vaccine early in 2011 with the support of GAVI, followed by DRC which introduced PCV-13. By 2011, South Africa switched to PCV-13, which offers a slightly broader protection against other serotypes of pneumococcal diseases [18].

Three countries (i.e., Madagascar, Malawi and Ethiopia) in the sub-region were approved for GAVI support in 2009 and are planning to introduce pneumococcal vaccines between 2011 and 2012 [18]. Following the April 2011 round of applications, six more countries applied and five were approved (Mozambique, Tanzania, Uganda, Zambia and Zimbabwe) while Lesotho has to address some issues prior to getting approval.

2.4. Rotavirus vaccines

Rotavirus infections are the most common cause of severe diarrhoea in children globally [21]. WHO estimates that rotavirus infections account for about 15% of diarrheal deaths, with the largest number occurring in developing countries. It is against this background that the WHO recommended the introduction of rotavirus vaccines into routine childhood immunization [21].

The recommendation to introduce rotavirus vaccines, although initially supported by significant disease burden demonstrated in developed countries, was further endorsed for developing countries in 2009, following conclusive evidence of effectiveness demonstrated in trials from African and Asian countries [21].

2.4.1. WHO AFRO region

By 2010, only 1 out of the 46 WHO AFRO countries had introduced rotavirus vaccine into routine immunization. Applications for introduction of rotavirus vaccines have been submitted by an additional 17 countries in the region (i.e., Ghana, Mali, Nigeria, Togo and Sierra Leone in West Africa and Angola, Burundi, Cameroon, Central African Republic and Congo in Central Africa) [17].

2.4.2. ESA sub-region

Of the 79 countries in the ESA sub-region, rotavirus vaccination has only been introduced in South Africa. The country introduced rotavirus vaccination simultaneously with PCV, as well as inactivated polio and acellular pertussis containing pentavalent (DTPa-IPV/Hib) vaccination in 2009 [18]. To date, none of the 13 GAVI funded countries of the sub-region have introduced rotavirus vaccines. There is however an expectation for an increasing number of countries worldwide to introduce rotavirus vaccines in the near future [9]. Countries that have submitted applications for GAVI to introduce rotavirus vaccine in the sub-region are Ethiopia, Eritrea, Kenya, Madagascar, Malawi, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe [17]. Out of these countries, Ethiopia, Madagascar, Malawi, Rwanda and Tanzania have been approved for support.

Based on previous experiences of serious adverse events of intussusception with Rotashield™ rotavirus vaccines, there is a need to strengthen surveillance of adverse events following immunization. The challenge is that intussusception is not a notifiable condition in most countries and may go undetected if surveillance is not strengthened and clinicians are not sensitized accordingly.

2.5. Human papillomavirus vaccine

Following recognition of the importance of cervical cancer and other HPV-related conditions as global public health problems, the WHO recommended in 2009, the introduction of HPV vaccines to national immunization programmes. This was to be considered if introduction was programmatically feasible and sustainable funding is available [22].

Although uptake of HPV vaccines in routine immunization in developed countries is increasing, there is currently one country (Rwanda) among the 19 in the sub-region that has introduced HPV vaccine nationwide following HPV vaccine donation and support from a vaccine manufacturing company in April 2011 [22]. However, the focus for GAVI is currently on the accelerated introduction of pneumococcal and rotavirus vaccines in an effort to reduce mortality in children under 5 years.

2.6. Post-introduction evaluation of new vaccines

WHO recommends that countries that have introduced new vaccines should conduct post introduction evaluations (PIE) 6–12 months after introduction to assess impact of new vaccines introduction on immunization programmes and learn lessons for future vaccines introductions [23]. In the recent past, a number of countries in East and Southern Africa have conducted PIE activities [23]. These countries include Ethiopia in 2007, Zambia in 2009, Rwanda, Swaziland, Zimbabwe and Lesotho in 2010, and South Africa, Tanzania, and Botswana in 2011.

3. Challenges and proposed way forward

It is clear that in order to achieve the targeted MDG’s of reduction of child mortality, there is an urgent need for countries to upscale efforts to reach more children with life saving vaccines in line with GIVS. About 23 million children remain unreached with traditional vaccines while many developing countries still need support to introduce new vaccines against pneumonia and diarrhoea [1, 8].

3.1. Competing priorities

Many developing countries are faced with large burdens of competing priorities like TB and HIV/AIDS. This means that although countries may be aware of the need to prioritize immunization programmes, there is difficulty in ignoring the more pressing priorities, given the current economic climate and limited resources available for health in countries. It should however be emphasized though that the majority of HIV/AIDS patients are co-infected by the same vaccine preventable pathogens responsible for the commonest causes of death like pneumonia and diarrhoeal diseases.

3.2. Decision making for introduction of new vaccines

Immunization and vaccines, although amongst one of the most cost-effective public health interventions, are not free. With the development of new and more expensive vaccines, the cost of immunizing one child was reported to have risen from an average of US $ 6.00 per live birth in 2000 to US $ 18.00 per live birth in
2010. The cost is furthermore projected to rise to about US $ 30.00 per live birth with new vaccines like pneumococcal and rotavirus beyond 2010 [8]. Reasons for the rising costs are not only from procurement of initially expensive new vaccines, but also the cost of expanding cold chain as well as hidden costs of introducing vaccines through staff training, more frequent distribution of vaccines, and expanding social mobilization and surveillance systems.

There is sufficient data to confirm cost-effectiveness of immunization programmes, as well as the worth of investing in immunization even with the rising cost [8]. There is therefore a need for the WHO and UNICEF to support countries to make a case for introduction of new vaccines through provision of cost-effectiveness information and tools that illustrate the value for money [8]. The decision to introduce new vaccines, although predominantly political, can be assisted to be more rational and transparent through thoughtful analysis [25].

3.3. Need for surveillance systems to support new vaccine introduction

Lack of sound surveillance systems and burden of disease data can negatively impact on the desire to introduce new vaccines. It is important for countries to build on some of the relatively well established existing systems like Accelerated Disease Control systems for polio, measles and integrated disease surveillance and response (IDSR) to consolidate some valuable information about disease burden. Absence of disease burden information alone should, however, not be a reason to not introduce vaccines as similar countries in the region can be used as a proxy [26].

3.4. Additional important logistical considerations that will impact on cost of introducing new vaccines

Although there is anticipation of a drop in current new vaccine prices as the demand increases, the current cost of vaccines may not be desirable for developing countries [8]. With the current packaging and presentation of new vaccines, UNICEF estimates that introduction of pneumococcal, rotavirus and human papillomavirus vaccines will need additional storage capacity of 100 cm$^3$ amounting to between US $ 1.00 and US $ 20.00 per child in the birth cohort, depending on the equipment requirements [27]. This is escalated by additional costs of training of staff, distribution of vaccines and logistics, social mobilization activities, updating and printing of data recording and reporting tools, and other key activities.

3.5. Need to sustain current routine immunization gains through high routine coverage

More vaccines with potential benefit to populations will be available in the future. Countries should not only evaluate disease burdens and prioritize new vaccine introduction, but they have to equally assess their capacity to introduce them. New vaccines introduction can rejuvenate the programme and increase coverage to more diseases, but this should not be done at the expense of already poor functioning programmes. This is why GAVI required a minimum coverage of 50% for DTP3 as a criterion for funding new vaccines, which has since been increased to 70%. This is based on the recognition that fixing current problems may be more important than introducing new vaccines [25,27].

3.6. Sustainability and ownership of immunization programmes through technical and financial support

Indeed with GAVI support many countries have scaled up efforts to reach more people with vaccines in line with GIVS. The escalating cost of vaccinating a child and the expectation for countries to take over some of the immunization budgets will make the need for cost-effectiveness studies more urgent [8,27]. The cost of new vaccines from international markets, for non-GAVI funded countries, is also increasing. Previously able countries may also face some financial constraints in sustaining immunization programme budgets and will need to be assisted in rectifying disparities in cost of vaccines [7,21].

GIVS emphasises the crucial role of financial commitment and ownership of immunization funding by countries in order to aid long-term sustainability of programmes. According to GAVI, there is clear marked improvement in countries fulfilling their commitment to co-financing of vaccines, as illustrated by 90% of the 46 WHO AFRO countries having honoured their co-financing commitment in 2009 [26]. In the progress report presented at the 64th World Health Assembly of 2011, preliminary MPV’s data analysed demonstrated that a growing number of countries had a budget line item for immunization. This analysis showed that average figure per live birth spent for immunization had increased from US $ 6.00 in 2000 to US $ 25.00 in 2008, and was expected to rise further in order to accommodate new vaccines [8]. This indicated the urgent need by WHO, UNICEF and partners to explore more favourable strategies of reducing vaccine prices.

3.7. Weak health systems hamper progress to achieve high immunization coverage

In support of the urgent need to implement the GIVS goal of attainment of MDG’s, GAVI has strengthened its support to health system strengthening, by allocating funding to assist countries to address weaknesses in health systems [28]. However, as guided in GIVS, introduction of new vaccines has presented opportunities to strengthen health systems through procurement of cold chain equipment and expansion of cold storage capacity, building of infrastructure, staff training, and other ways.

3.8. Data management for monitoring programme performance and decision making

Use of immunization coverage data to monitor programme performance in a timely manner remains a challenge in many countries [7,24]. The quality of data needs closer attention as well as strengthening of surveillance systems for adverse events following immunization. For introduction of new vaccines, the global framework for immunization monitoring and surveillance (GIFMS) outlines steps in ensuring the use of coverage data and surveillance of targeted disease burden to monitor programme performance. Documentation of number of children vaccinated and trends in disease burden through surveillance is crucial [29]. Further availability of support through implementation of data quality self-assessment tool should be utilised to improve data quality [30].

3.9. Integrating immunization with other health interventions

In accordance with GIVS, as vaccines do not protect against all diseases, there is need to integrate immunization with other proven life saving interventions to maximize the impact on overall disease burden and child mortality. The recognition of immunization as a valuable intervention and necessary part of overall disease control as illustrated in the recently launched Global Action for Prevention and Control of Pneumonia (GAPP) [31]. This ensures that decision makers do not view immunization as vertical programmes competing against other conditions, but as an integral enabler for child survival. Other integrated programmes include the comprehensive WHO/UNICEF Diarrhoea Control Strategy.
(November 2009) and the comprehensive Cervical Cancer Control Strategy [32,33].

4. Conclusion

There is no doubt that immunization remains amongst the most cost-effective tools and has a valuable role to play in facilitating the attainment of specifically MDG 4. With available new vaccines against diarrhoea and pneumonia, there is a better chance to accelerate reduction of child mortality and positively influence quality of life for all, through implementation of the clear framework outlined in the WHO and UNICEF GIVS.

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References

Review

The decision making process on new vaccines introduction in South Africa

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A B S T R A C T

South Africa has a functional decision making process for the introduction of new vaccines; with an established National Immunisation Technical Advisory Group (NITAG), referred to as National Advisory Group on Immunisation (NAGI). South Africa has played a leadership role in the African continent with introduction of new vaccines, which dates back to 1995 with the introduction of hepatitis B, followed by the Haemophilus influenzae type b in 1999 and recently the national roll out of the pneumococcal conjugate and rotavirus vaccines in 2009.

NAGI has the responsibility to deliberate on key policy issues as part of the process for decision making on the introduction of new vaccines. In developing recommendations NAGI considers: disease burden, cost effectiveness, and the impact on the Expanded Programme on Immunisation (EPI). Although guidance and recommendations from WHO are considered, the decision to introduce a new vaccine in South Africa is based on local data. NAGI recommendations are presented to the National Department of Health (NDOH). The NDOH pursues the matter further through the involvement of provinces. When an agreement has been reached to accept the NAGI recommendations, the NDOH seeks funding from the Ministry of Finance (MOF). Once funds are available, the new vaccines are implemented by the immunisation programme.

Although there is an established functional system for decision making in South Africa, some areas need to be addressed. A system should be developed to allow the NDOH, NAGI and the MOF to engage in the deliberations on financial and economic impact of new vaccines. It is further recommended that a committee be established that will assess the programmatic issues to weigh the potential benefits of a new vaccine. Furthermore, political commitment should support the immunisation programme and strengthen it so that it can make an impact in the achievement of the Millennium Development Goal no. 4 of reducing child mortality.

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1. Introduction

In April 2009 the Expanded Programme on Immunisation (EPI) in South Africa (SA) rolled out the national implementation of two new vaccines: pneumococcal conjugate vaccine (PCV) and rotavirus vaccine (RV). SA was the first country in the African continent to introduce the two new vaccines. PCV has now been introduced in other countries in Africa like Kenya and Rwanda that are supported by the Global Alliance for Vaccines and Immunisation (GAVI). However, as of October 2011 SA remains the only country in the WHO Africa region that self finances these vaccines [1].

The introduction of PCV and RV is a significant public health milestone for the country and the continent. Furthermore, it points to the leadership role that South Africa has taken in the continent with the introduction of new and underutilised vaccines, dating back to 1995 with the introduction of Hepatitis B (Hep B) and in 1999 with Haemophilus influenzae type b (Hib) vaccines [2].

The decision to introduce a new vaccine is complex and influenced by a number of factors including social, political concerns and programmatic issues. WHO recommends a decision making framework for new vaccine introduction, which considers policy and programme issues [3]. Policy issues consider the disease burden, vaccine safety, effectiveness, the burden and benefits ratio as well as cost-effectiveness. There are a number of decision making tools developed, some specifically for policy decision on the use of PCV; these include Pan American Health Organisation's (PAHO's) Trivac model, the Pneumo ADIP model and the Glaxo Smith Kline (GSK) SUPREMEs model [4].

Considering the complexity of the introduction of new vaccines and that such decision relate to an important public health...
programme; it is crucial that these decisions which establish immunisation policies are well informed, unbiased, evidence based and are locally relevant. This has been the basis of the formation of National Immunisation Technical Advisory Groups (NITAGs) in many countries; particularly in developed countries where these groups are well established [5]. South Africa has a functional NITAG, referred to as the National Advisory Group on Immunisation (NAGI). NAGI is effective as a source of information and an advisory body to the National Department of Health (NDOH) in South Africa. This is evidenced by its major role in the recent introduction of PCV and RV into the South African Expanded Programme on Immunisation (EPI-SA) [6].

This paper examines the decision making process on new vaccines introduction in South Africa. It outlines the process focussing on NAGI’s role, the NDOH decision making structures and other important factors that facilitate decision making. It points at some weaknesses in the decision making system and provides recommendations.

2. NAGI and a brief overview of decision making on new vaccines

In South Africa the introduction of new vaccines comes from the recommendations of NAGI, a group of experts that advises the Department of Health on vaccination issues. NAGI’s recommendations are presented to the technical head of the NDOH, the Director General.

NAGI was established in 1993 to advise the NDOH on technical matters and policy issues relating to vaccination. It is composed of experts from different fields that bear on vaccination including: microbiology, virology, public health, epidemiology, infectious disease control, immunology and paediatrics [6].

NAGI’s primary responsibility is to make recommendations on the introduction of new vaccines, immunisation policy, vaccine formulations and to advise on control of other infectious diseases. NAGI has been functional and effective in its mandate; as it has been instrumental in the introduction of: Hep B vaccine, Hib vaccine, and PCV and RV. In 2009, NAGI also recommended the introduction of injectable polio vaccine, which is in combination with acellular pertussis, diphtheria, tetanus and Hib [6] (Table 1).

NAGI has clear terms of reference (TOR) which include the collation of necessary literature to aid decision making and to identify key research areas that relate to immunisation. NAGI’s function is mainly advisory; their recommendations are not legally enforceable [6].

While NAGI decisions on new vaccine introduction are influenced by WHO recommendations, NAGI has ensured that WHO recommendations and strategies are adapted within the local context in accordance with the TOR. An example is the decision NAGI took to recommend that PCV be given at 6 weeks, 14 weeks and at 9 months (Table 1). This decision was based on the high prevalence of HIV within the South African population and provides a booster dose later in the first year of life. The two plus one schedule was not part of the WHO recommended schedule but was implemented into the national EPI schedule.

3. Key policy considerations

The key areas for taking a rational informed technical decision on the policy of introducing a new vaccine requires information on the following areas: disease burden, vaccine safety and effectiveness, vaccine cost and the expected net impact on the immunisation programme and the health sector. The following areas are briefly discussed in relation to NAGI’s deliberations and collation of relevant information necessary for developing recommendations.

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
<th>How and where</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>BCG (1)</td>
<td>Intradermal, right arm</td>
</tr>
<tr>
<td>6 weeks</td>
<td>OPV (0)</td>
<td>Drops, oral</td>
</tr>
<tr>
<td>10 weeks</td>
<td>RV (1)</td>
<td>Liquid, oral</td>
</tr>
<tr>
<td>14 weeks</td>
<td>DTaP-IPV//Hib (1)</td>
<td>IM, left thigh</td>
</tr>
<tr>
<td>9 months</td>
<td>Hep B (1)</td>
<td>IM, right thigh</td>
</tr>
<tr>
<td>18 months</td>
<td>PCV (1)</td>
<td>IM, right thigh</td>
</tr>
<tr>
<td>6 years (Both boys and girls)</td>
<td>Td (1)</td>
<td>IM, left arm</td>
</tr>
<tr>
<td>12 years (Both boys and girls)</td>
<td>Td (2)</td>
<td>IM, left arm</td>
</tr>
</tbody>
</table>

Table 1 Recommended immunisation schedule for infants and children within the South African Expanded Programme on Immunisation (EPI-SA) since April 2009.

*Rotavirus vaccine should not be given after 24 weeks.

The Disease Burden and Public Health Priority of the condition targeted with a new vaccine is a primary consideration. The issues to be addressed relate to the incidence, the morbidity and mortality from the condition, and the public health significance of the condition. It is not just the numbers affected but is also about the severity of the condition.

NAGI contributes a major role in the collation of relevant country specific literature and deliberates on disease burden with a focus on: incidence rate, mortality, disability adjusted life years, hospitalisation and epidemiic potential [6].

South Africa had a number of studies conducted on the disease burden of pneumonia. Furthermore, the study on the impact of 9 valent pneumococcal conjugate vaccine was conducted in Soweto, South Africa with results published as early as 1999 [7]. Similarly there were a number of disease burden studies on rotavirus and the WHO multi-centre trial on rotavirus vaccine included South Africa, with a research site at the University of Limpopo Medunsa campus.

Efficacy and Safety are of primary importance and relate to licensure. This area is the responsibility of the National Regulatory Authorities. Most products would have gone through a WHO prequalification process and would have been licensed in the country of origin. South Africa has the Medicines Control Council (MCC), the National Regulatory Authority which requires vaccines and other pharmaceuticals to be registered before they can be used in the country. In the case of PCV and RV, both vaccines had been recently registered with the MCC when they were incorporated into EPI in 2009. Furthermore, MCC requires that all batches of vaccines should be pre-tested by the National Control Laboratory before release [8].

The Cost and Fiscal Impact is an important area for discussion. Immunisation programmes have traditionally represented the best buys in the health sector as significant health outcomes were achieved per less than 1 US$ per dose. Although still cost effective, new vaccines are much more expensive [9].

SA is not GAVI supported and the full cost of vaccination is financed through taxpayers’ contributions. It is estimated that with the introduction of RV & PCV vaccines, the cost of a fully immunised child in SA has increased 10-fold [10]. This emphasises the need to carefully analyse the costs and benefits of adding new vaccines.
and their long term potential impact on national budgets to ensure financial sustainability of the revised schedule [11].

The contributions to NAGI on economic aspects like cost-effectiveness studies or estimates are provided by NAGI members with specific interest in the field. For example, the SUPREMES model was used in conjunction with WHO guidelines to make a decision regarding the cost effectiveness of PCV. NAGI also considered the cost utility, and the impact of herd immunity for the whole population. However, the effects of serotype replacement could not be incorporated. This may be a limitation of the decision model [4].

The Impact: The difference that a new vaccine will make is dependent on a number of factors including: disease burden, vaccine effectiveness, of the new vaccines and the level of immunisation coverage. NAGI recommendations aim to support the Department of Health to strengthen EPI and other child survival strategies. The focus was on how to maximise the benefits of PCV and RV, considering SA’s heavy burden of HIV/AIDS and that the HIV infected carry a high proportion of the invasive pneumococcal disease burden [12].

4. Programme considerations

Programme factors may dictate that the introduction of a new vaccine be postponed till problems are solved, even when policy issues are in favour of new vaccine introduction and funds are available. It should be noted that programmatic issues are not part of NAGI’s decision making process. The Department of Health has to deliberate on the feasibility and programme implications. Four areas are briefly discussed.

Programme strength: The main question addressed here is whether the immunisation programme is strong enough to effectively absorb the introduction of new vaccine. Programme strength refers to immunisation coverage, cold chain capacity and functioning, staffing, supervision, surveillance systems for the diseases covered by the programme and surveillance for adverse events. If an immunisation programme has serious weaknesses like: staff shortages, poor supervision, lack of planning and budgeting at one or more levels of service delivery (e.g. district or provincial level) it may be best to first address these challenges before introducing a new vaccine.

Immunisation coverage is a good indicator of the functioning of an immunisation programme. When the new vaccines were introduced in 2009, coverage figures at national level were: DPT-Hib 3rd dose was 100%, fully immunised coverage was 89% and measles 1 coverage was 91% [13]. Furthermore, all provinces had EPI managers posts filled and practically all technical EPI posts at national office were filled. EPI’s strength at that time was considered to be strong enough to absorb the new vaccines.

The vaccine presentation and the schedule of a new vaccine may complicate storage and administration. For example, the following parameters are considered: is the vaccine a single antigen or a combination with other vaccines, a mono-dose or multi-dose vial, does it need reconstitution or it comes as pre-filled syringe, or is it given orally or by injection? If the proposed administration schedule fits into the current schedule, there will be no additional visits by clients.

Both PCV and RV are mono-doses and single antigens. This had serious implications in that there were significant extra cold chain requirements and there were extra steps of work per child immunised. Furthermore, the initial rotavirus vaccine packaging and presentation had challenges; it was bigger and required reconstitution with a number of steps in that process.

Programme schedule: Both RV and PCV fitted well with the 6, 10, 14 weeks schedule used in South Africa. However, for practical reasons and as described earlier, there was an adjustment to the generally recommended schedule. Subsequently in the revised schedule, RV (Rotarix) is given at 6 weeks and 14 weeks and PCV is given at 6 weeks, 14 weeks and the third dose at 9 months together with first dose of measles (see Table 1).

Vaccine supply. Current and future supply issues and the projected demand for a new product are important considerations. A number of market forces particularly early in the production of a new product may determine the availability of the product. This needs to be carefully discussed with the: manufacturer/s, other potential suppliers, local experts and international organisations like UNICEF and WHO.

The NDOH addressed this area for PCV and RV and meetings were held with the suppliers through the national distributor, The Biovac Institute. The Biovac Institute is a vaccine company, which has a Public Private Partnership (PPP) agreement with the NDOH to procure vaccines for the South African population [14]. Biovac has the responsibility to ensure that suppliers have enough stock for an uninterrupted supply of vaccines. For the new vaccine supply, Biovac liaised with the suppliers and there were no vaccine shortages. However, due to stock availability and the change to the newer RV presentation, the introduction of RV had to be delayed to August 2009, three months later than the planned joint introduction with PCV, which was introduced in April 2009.

Once a policy decision has been taken to introduce a new vaccine, the NDOH deals with programmatic issues. With no external independent support, this is often an area that is neglected and poorly assessed. With PCV and Rotavirus vaccines some programme constraints and challenges were experienced including cold chain capacity constraints at district depots and upgrading of data collection tools and indicators which affect data quality. A technical committee that assesses programme issues, made up of advisers and EPI staff would be ideal to address this limitation. Such a committee would also take up the responsibility of working on strategies to exploit opportunities presented by new vaccines to strengthen EPI, a point brought up by Duclos et al. [15].

5. The decision making process for NDOH, Provinces and Ministry of Finance

In the decision process for new vaccine introduction, the first stage is for NAGI to make recommendations to the NDOH to include the new vaccine. The second stage is for the Minister, Director General and other senior officials in the NDOH to deliberate on the issue and weigh the potential benefits.

The third stage is that of presenting the recommendations to the National Treasury of the Ministry of Finance (MOF), particularly when a significant financial commitment is to be made. The Minister of Health normally engages the Minister of Finance, to ensure availability of funds through the National Treasury. The National Treasury has the services of a health economist who also considers the cost utility and the fiscal impact and national budgetary priorities of introducing new vaccines. However there is no forum for Treasury to discuss with NAGI any concerns or vice versa.

In the fourth stage the recommendations on a new vaccine are taken to the National Health Council (NHC). The NHC is comprised of the Minister, the Provincial Ministers of Health, the Director General of NDOH and the Provincial Heads of Health. This stage is critical, as the Provincial Departments of Health have the responsibility to implement national policies and if in agreement, it is during this phase that the NHC will discuss an implementation plan. Once the NHC approves the recommendation, this means that provinces have committed themselves to implementation of the new vaccines.
Following approval by the NHC, the EPI unit together with provincial counterparts have the responsibility to implement the decision. Challenges are faced as they arise with support of local experts, the World Health Organisation and UNICEF. The actual implementation is a huge undertaking. Many areas need additional resources and revision of tools like: cold chain equipment; data records, immunisation registers, patient held records; training; social mobilisation, advocacy, surveillance for the targeted conditions and for adverse events following immunisation.

6. Other factors that influence decision making in South Africa

Over above the process described with introduction of a new vaccine, there are other factors that have an influence and affect the process. These factors may either facilitate, hinder or bear pressure on the Department to introduce a particular antigen into the EPI.

The position and the responsibilities of NAGI should be understood and respected by the NDOH, specifically the offices of the Director General and the Minister. This allows for creation of clear communication channels for NAGI and for presentation of NAGI recommendations to the Department. If this is not the case, the role of NAGI in influencing decision making is diminished, which has occurred in the past. However, during the introduction of PCV and rotavirus vaccines there was a clear link between the higher offices of NDOH and NAGI as the minister’s advisor served in NAGI as an ex officio member. This significantly facilitated the process.

Political commitment plays a significant role in the introduction of new vaccines in SA and it did for the introduction of PCV and rotavirus vaccines. The Minister of Health showed clear commitment; which was demonstrated by an announcement during the 61st WHA in May 2008 that SA will introduce PCV and rotavirus vaccines.

GAVI’s position and plans relating to new vaccines have a significant influence. If GAVI has started to support eligible countries, there is increased pressure for SA to keep abreast. When South Africa announced its plans to introduce the two new vaccines in 2008, GAVI had expressed the intention to support the introduction of PCV for some countries in Africa.

The SA media has to some extent played a role in influencing decision making. When a vaccine has been launched in the private sector; the media directly engages the Department on why the vaccine is not available at public facilities. The media did this with PCV and the NDOH had to respond.

Professional groups and some professional activists have a potential to influence decision making. Although they did not play much role for PCV and rotavirus vaccines; the introduction of Hib vaccine in 1999 is believed to have been influenced by pressure from paediatricians. This probably did not happen for PCV and RV vaccines because political commitment came much earlier than expected.

7. Lessons learnt

One of the main lessons learnt in the introduction of new vaccines in South Africa is regarding the availability of funds to procure the vaccines and the sustainability of the revised schedule. The main weakness in South Africa’s decision making process is that the advisory body, NAGI, is not fully informed on the budget and the funds available for the new vaccines. So with latest introduction, the recommendations were accepted by the Department yet initially insufficient funds were allocated by the MOF. A system where there is transparency and budgetary information is shared with NAGI would be desirable. NAGI could then adjust recommendations to include budget limitations. This was not the case. All three parties acted independently and the EPI unit had to work with financial constraints.

Other lessons learnt relate to issues already raised, on the need to have a specific committee on programmatic issues and on recognised channels of communication.

8. Conclusion and recommendations

South Africa has an established functional system for decision making on the introduction of new vaccines. Nevertheless, there are weaknesses which need to be addressed. A system should be developed to allow the NDOH, NAGI and the MOF to deliberate on financial and economic impact of new vaccines. This will ensure that NAGI decisions consider financial constraints faced. It is further recommended that NAGI has a health economist or a subcommittee, specifically for health economics issues and consult with National Treasury.

Programmatic problems need a vigorous appraisal system conducted by a committee made up of independent advisors and EPI staff. The committee should also be tasked with ensuring that the introduction of new vaccines is used to strengthen the immunisation programme and other child survival interventions. Political commitment to ensuring an effective immunisation programme should be maintained and be proactive in its support for EPI to make an impact in the achievement of the Millennium Development Goal no. 4 of reducing child mortality.

Declaration of potential conflict of interest

The authors hereby solemnly declare that they have no commercial or any other interest that may in any way be relevant to the work published. The authors have received neither grant nor any form of financial support from any pharmaceutical company or any organisation that may have interest or a stake in the matters raised in this document. Authors have no conflict of interest in the matters raised.

References


1. Introduction

Acute severe dehydrating rotavirus diarrhoea remains a major contributor towards childhood mortality and morbidity worldwide [1]. Globally, rotavirus infection is estimated to cause 111 million episodes of gastroenteritis requiring home care, 25 million clinic visits, 2 million hospitalisations and approximately 453,000 deaths in children under 5 years of age on an annual basis [2,3]. Approximately 50% of 453,000 deaths occur in Africa with an estimated 232,000 deaths [3]. The burden of rotavirus disease is significant in both developed and developing countries where almost all children will have experienced rotavirus gastroenteritis by the age of 5 years, and 1 in 5 will visit the clinic, 1 in 65 will be hospitalised and approximately 1 in 293 will die [4]. In South Africa, diarrhoeal diseases are ranked the third major cause of childhood mortality in children less than 5 years where the majority of deaths are among black African children [5]. Rotavirus has been documented as causing a third of all diarrhoea admissions to the hospital [6].

In 2009, the Global Surveillance Rotavirus Network showed that rotavirus was detected in a median of 41% (range: 16–57%) of hospitalised children less than 5 years in 9 African countries including Cameroon, Ethiopia, Ghana, Kenya, Tanzania, Uganda, Zambia and Zimbabwe [7,8]. The median rotavirus detection rate is however slightly lower at 35% (range, 23–48%) in a similar cohort of South African children [6,9,10]. According to the recent estimates the incidence of diarrhoeal disease in South Africa is 111.8 per 1000 children less than 5 years of age [11]. If we multiply the median rotavirus detection rate of 35% with diarrhoeal incidence, it is estimated that 39/1000 children less 5 years will be infected by rotavirus infection in South Africa. The data from South Africa based on studies conducted at Dr George Mukhari hospital, a sentinel site at University of Limpopo teaching hospital in Pretoria, South Africa, has conducted rotavirus surveillance for >20 years.
2. Rotavirus epidemiology

2.1. Rotavirus transmission

Rotaviruses are highly infectious and relatively resistant to chemical disinfectants and antiseptics. It is difficult to control rotavirus infection because the virus is stable on environmental surfaces and are shed in high concentrations in the faeces of infected patients [12]. The primary mode of transmission is by the faecal-oral route, although the respiratory route has been suggested as an alternative mode of transmission [1]. Rotavirus spreads easily in circumstances of overcrowding and poor hygiene. The virus can be spread through contaminated food or water, direct contact with contaminated surfaces and person-to-person contact [12,13]. Transmission of rotavirus can be easily facilitated in children’s day care centres or family day care homes through frequent exposure of susceptible hosts. Studies have shown that nosocomial rotavirus infections in paediatric wards and hospital nurseries are quite frequent [14,15].

2.2. Clinical features

The symptoms of rotavirus infection vary from asymptomatic, mild to severe with occasional fatal dehydrating illness. The incubation period in young children is 24–48 h post-infection [15]. The classic acute gastroenteritis associated with rotaviruses is characterised by either the onset of vomiting, which lasts for 1–2 days of watery diarrhoea, which persists for approximately 3–8 days. The clinical symptoms of rotavirus diarrhoea vary from child to child. However, rotavirus infections cause severe diarrhoea and are more likely to be associated with dehydration up to 10–20 bowel movements per day. This is often accompanied by abdominal cramps. In some cases, children may experience a cough and runny nose [16]. Rotavirus infections can be fatal if left untreated. The most frequent cause of death is severe dehydration and electrolyte imbalance. In a study done in Kenya and Ghana, non-bloody diarrhoea, vomiting and life threatening complications were more frequently detected in children infected with rotavirus than with bacterial pathogens [17,18].

Rotavirus infections may also be asymptomatic although the lack of symptoms may be more common in neonates and infants or older children with previous history of rotavirus infections [15].

2.3. Seasonality of rotavirus infection

Climatic conditions have a major influence on the incidence of rotavirus infections, especially in regions where there are seasonal changes. In temperate climates, rotavirus disease occurs during epidemic peaks in the cooler, drier months. In the northern hemisphere, rotavirus tends to be predominant between December and March while in the southern hemisphere rotavirus occurs between May and September [19–22]. Many studies have shown significant winter seasonality of rotavirus infection, although endemic and sporadic cases may occur during warmer months. In the United States, Europe, India, Asia, Republic of Korea and Japan, hospitalisation rates of rotaviruses peak during winter months [19–22].

In tropical regions, seasonal rotavirus gastroenteritis patterns are less pronounced and rotavirus infection occurs throughout the year with minor increases during the drier season [23]. In sub Saharan Africa, increased cases of rotavirus infection are usually experienced during the drier months of the year and a low rate of rotavirus infection during the wet season [7,17,24,25]. The recent seasonal rotavirus infection data in the tropical regions of Africa showed a marked increase of rotavirus diarrhoea during the dry season [7].

Rotavirus infections in Southern Africa display a distinct seasonal pattern with epidemic peaks occurring predominantly in the cooler and drier winter months of the year [24,25]. The seasonal trend of rotavirus infection in South Africa displays consistent annual rotavirus gastroenteritis in winter peaks. The proposed mechanism underlying seasonal variation probably involves the interplay of many factors including survival of virus in the environment, low indoor relative humidity, higher airborne transmission, physiological effects on the host and the degree of crowding during the winter season [26].

2.4. Age distribution of rotavirus

Worldwide, epidemiological studies indicated that all children are infected with rotavirus before their third birthday. In South Africa, the burden of disease study showed that a large proportion (90%) of children less than 24 months of age admitted or visiting the outpatient department were infected with rotavirus and rotavirus infection occurs as early as 2 months of age [9]. The highest prevalence of rotavirus infection occurred among children aged 3–17 months old [9,24], compared to the European countries where the highest incidence of rotavirus infection is found in children aged 6–23 months [27]. In addition, the peak incidence rate of symptomatic rotavirus infection in many industrialised countries is from 6 to 18 months whereas in developing countries children tend to become infected earlier, i.e. below 6 months of age [28].

3. Laboratory diagnosis

The laboratory diagnosis and detection for group A rotavirus include; electron microscopy (EM), cell culture, variety of enzyme immunoassays (EIA), polyacrylamide gel electrophoresis (PAGE), reverse transcriptase polymerase chain reaction (RT-PCR) genotyping, real-time PCR and sequencing. African green monkey kidney cells (MA104 cell line) are commonly used for rotavirus isolation [1]. The EM is a reliable method used to detect rotaviruses, mainly due to their distinctive morphology, although most laboratories do not have this technology. The viral antigens can be detected using a variety of commercially available EIA and latex agglutination assays (rapid diagnostic test). However, the ELISA is the recommended test system due to its sensitivity and ease of use in virtually all hospital laboratories [7]. PAGE has been used to determine the genomic diversity of rotavirus by studying distinct migration patterns of the 11 segments of dsRNA. The RT-PCR genotyping assays for the VP4 and VP7 genes are widely utilised for typing the circulating rotavirus strains [1].

4. Rotavirus virology

Rotaviruses are classified within a Reoviridae family, the segmented double stranded (ds) RNA viruses. The genome codes for six structural viral proteins (VP1–VP4, VP6 and VP7) and six non-structural proteins (NSP1–NSP6). The viral particle is surrounded by triple layered capsid; an inner core layer composed of shell viral protein VP2 and enzymes VP1 and VP3, an intermediate layer of VP6 and outer layers made up of VP7 (major outer capsid) and VP4 (outer spikes) [1]. The inner capsid VP6 antigenic specificity classifies rotaviruses into seven serogroups (A–G). Rotaviruses are further classified into different P and G types based on the two outer capsid proteins: VP4 (protease-sensitive) and VP7 (glycoprotein), respectively. These proteins independently elicit protective neutralising antibodies [1]. However, the rotavirus particle consists of more than just the inner and outer capsid proteins and, therefore, a new rotavirus classification and nomenclature system identifying
genotypes for each of the 11 gene segments was proposed [29]. Currently, among group A rotaviruses, the following genotypes have been identified VP7: 27 G, VP4: 35 P, VP6: 116, VP1: R9, VP2: C9, VP3: M8, NSP1: A16, NSP2: N9, NSP3: T12, NSP4: E14 and NSP5/NSP6: H11 genotypes [30].

5. Rotavirus genetic diversity

The molecular epidemiology of rotavirus strains is complex; the strains likely to circulate each year cannot be entirely predicted. Hence, the circulating rotavirus strains vary from year to year, season to season and region to region [31]. The observed phenomenon could be explained by the role of the selective pressure of serotype specific antibodies [32] and the segmented nature of the rotavirus genome that could easily facilitate reassortment between different strains during mixed infections. Mixed genotype infections might result in inter- and intra-genotypic diversity or inter-genogroup strains. Novel rotavirus strains or unusual strains previously isolated from animals have also been detected in humans [33,34].

Surveillance of rotavirus strains have shown five group A rotavirus strains which are frequently detected globally; i.e. G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] [35]. These strains are often referred to as common or predominant strains and are responsible for 88.5% of infections in North America, Europe and Australia, while the same strains represent 68% and 50% of infections in South America and Africa, respectively [35]. A large majority of rotavirus infections in developing countries display worldwide unusual strains, mixed genotype infections and untypeable strains [36].

Since 1998, rotavirus surveillance studies were conducted in 25 African countries to monitor circulating rotavirus strains [7,9,37–42]. Between 1983 and 1989, the G1-G4 associated with P[8] and P[4] were the most common strains detected in South Africa, Gambia, Nigeria, Kenya and Central Africa. Untypeable rotavirus strains represented 26% and mixed infections 1.8% [25]. The results from the three African Rotavirus Surveillance Network Workshops (AFR-RSN) from 1996 to 1999, representing countries in the North, West, East and Southern Africa supported the idea that G1 was the most predominant strain, followed by G2, G3, G9, G4 and G8 rotavirus strains [43]. Further studies from the 2006–2008 African Rotavirus Surveillance Network Workshops also identified G1P[8] and G2P[4] genotypes as the most common strains in 11 countries [7]. In Africa, a large proportion of the circulating rotavirus strains carry the unusual G8 and/or P[6] epitopes and are considered epidemiologically important strains in the region [7,40,43–45]. Compared to industrialised countries such as Europe and North America, there is a relatively high incidence of P[6] strains identified in Africa [7,40].

The G12 rotavirus strain was first detected in humans in 1987 in Philippines, a decade later, the strain was shown to be the most important emerging genotype worldwide [46–49]. In Africa, G12 rotavirus strains were first detected in South Africa at Dr George Mukhari Hospital in 2004 and since then, have been detected at an increasing rate in the Southern Africa (Zambia and Zimbabwe), East Africa (Kenya, Ethiopia and Uganda), Central Africa (Cameroon and DRC) and West Africa (Togo and Burkina Faso) [7,49].

During the past 30 years in South Africa, the G1-G4 associated with P[8] and P[4] have been the most common strains detected, as evidenced by recent data from rotavirus burden of diseases study conducted at Dr George Mukhari Hospital (Fig. 1). These strains were responsible for 49% of all rotavirus infections, while 51% was associated with mixed genotype infections, worldwide uncommon strains and untypeable strains. Interestingly, there was no correlation observed between the circulating genotypes, clinical outcomes of rotavirus infection and hospitalisation rates. The relative prevalence of the worldwide common rotavirus strain G1P[8] showed year to year variation, and the strains were further replaced by outbreaks of the G2P[4], G3P[8], G9P[8] and G4P[8] rotaviruses. While the distribution of G1P[8] rotavirus strains persisted overtime, the G2P[4] rotavirus strains showed a cyclic peak every 3–4 years (Fig. 2).
6. Prevention and control

6.1. Treatment

Currently, there is no specific treatment for rotavirus gastroenteritis except supportive care which involves management of symptoms. The patient is offered oral rehydration solutions (ORS) or intravenous fluid replacement to restore lost body fluids and electrolytes (sodium, potassium, bicarbonate). Oral fluids and supplementary nutrition can be provided to prevent dehydration. Dehydration can be life threatening if these electrolytes are not replenished swiftly. In addition, treatment of rotavirus diarrhoea with anti-rotavirus immunoglobulin of bovine colostrum origin is effective in controlling symptoms of rotavirus infection mainly in chronic or immunosuppressed individuals [50], although this is not routine practice in many developing countries affected by rotavirus morbidity and mortality.

6.2. Hygiene and sanitation

There is no significant difference between the rotavirus infections rate in industrialised as opposed to poor countries. Practising good hygiene such as hand washing, access to clean water and sanitation has shown to be partly effective to control rotavirus diarrhoea. Currently, rotavirus vaccines are considered as the effective intervention to either reduce or control the incidence of rotavirus disease [1].

6.3. Immunisation

Rotavirus vaccine development has consisted of different strategies, and of these, three vaccines have been licensed for global use to date. The first rotavirus vaccine to be licensed for routine use in 1998, rhesus-human rotavirus reassortment-tetravalent vaccine (Rotashield), was later withdrawn after about 9 months use in the USA because of its association with increased risk of intestinal intussusception [51]. The vaccine demonstrated high efficacy in developed countries and lower efficacy in developing countries [52,53]. Since the withdrawal of Rotashield, two additional vaccines; Rotarix® and RotaTeq™, have been licensed in more than 100 countries and these two vaccines have successfully been incorporated in national immunisation programmes of a number of countries [54]. Furthermore, the Lanzhou lamb rotavirus (LLR) vaccine, G1P[12] strain, has been licenced for use in China since 2001 [55].

Rotarix®, developed by GlaxoSmithKline Biologicals (Rixensart, Belgium), is a live human attenuated monoclonal G1P[8] rotavirus vaccine and its efficacy is based on heterotypic immunity. RotaTeq™, developed by Merck (Blue Bell, PA, USA), is a live attenuated bovine-human vaccine containing five reassortant strains with G1P[7], G2P[7], G3P[8], G4P[6] and G6P[8] specificity and its efficacy is based on homotypic immunity. Both these vaccines have shown a comparable protective efficacy (85–98%) in preventing severe rotavirus diarrhoea among children in developed countries, Latin America and Finland. However, lower efficacy rates were observed in developing countries of Africa (61.2–64.2%) and Asia (48.3%). Moreover, the vaccines were not associated with an increased risk of intussusception [56–61]. In 2009, the WHO SAGE recommended the inclusion of these rotavirus vaccines in all childhood immunisation programmes of the world [62].

7. Rotavirus vaccine within South African expanded programme on immunisation

Some of the pivotal studies which provided the policy makers including National Advisory Group on Immunization (NAGI) and National Department of Health with required information to make informed decision and facilitated the introduction of rotavirus vaccine into the South African Expanded Programme on Immunisation (EPI-SA) included the burden of disease (BOD) and strain surveillance, economic burden of rotavirus infection and clinical trials to assess the safety and efficacy of vaccine candidates.

7.1. Rotavirus burden of disease study

Although South African researchers have documented the epidemiology of rotavirus since the early 1980s [6,40,63], the BOD study provided comprehensive estimates and incidence of rotavirus disease requiring hospitalisation, contributed to baseline information against which to measure the impact of rotavirus vaccine after introduction, identified recent common rotavirus strains circulating in children less than 5 years (Fig. 1), and generated awareness on rotavirus for policy makers and health care workers [6,9]. The study began in 2003 and involved collection of stool samples from inpatient and outpatient children less than 5 years presenting with diarrhoea (Fig. 3). The study adopted a consistent systematic sampling approach and patient recruitment. Each year, the median and range of rotavirus detection rates were calculated among hospitalised and outpatient children. Overall, the results showed that rotavirus infections accounted for a quarter of all diarrhoeal hospitalisation each year with peak prevalence ranging from 56 to 78% during the cooler dry months of the year. The seasonal trends of rotavirus infection between 2003 and 2011 demonstrated the rotavirus epidemic season starting from May through July every year (Fig. 3). It was estimated that 23–25% of children less than 5 years of age hospitalised with diarrhoea were infected with rotavirus [6,9].

Between 2003 and 2005, the hospital-based burden of rotavirus gastroenteritis study estimated that one in every 43–62 children aged between birth and 2 years will likely be hospitalised for rotavirus diarrhoea. It was also estimated that 5.5% of all hospitalised children less than 5 years of age were infected by rotavirus [9]. Comparable results were obtained between 2007 and 2010 (Fig. 3). Similarly, data observed in the US estimated that rotavirus diarrhoea was associated with 4–5% of all diarrhoeal hospitalisation and one in 67–85 children less than 5 years would be hospitalised [8,64].

7.2. Economic burden of rotavirus infection

The BOD study at Dr George Mukhari Hospital was complemented by another study determining the direct and indirect medical cost of rotavirus diarrhoea at a tertiary hospital [65]. The direct medical costs of inpatients included hospital stay facility cost, hospital professional cost, laboratory diagnosis, personnel, overheads and medication, whereas the direct medical costs for outpatients were laboratory test and medications. The indirect medical cost included travel, other out of pocket cost incurred by the household as a result of diarrhoea and time lost from productive work by a guardian/parent. The estimated medical cost incurred for rotavirus gastroenteritis at the tertiary hospital was substantial. The mean direct and indirect costs of diarrhoeal cases included the rotavirus diarrhoea and rotavirus negative patients’ hospitalisation were estimated to be $784.61 and $535.53 respectively ($1 = R7.60). The large proportion of the cost was due to the tertiary nature of hospital services [65].

7.3. Rotavirus vaccines safety and efficacy trials in South Africa

The vaccine clinical trials that were conducted in Madibeng and Ga-Rankuwa district and Soweto, South Africa from 2002 to 2009 comprised phase II immunogenicity trials (2 versus 3 doses)
where Rotarix® was co-administered with routine EPI vaccines and either oral poliovirus vaccine (OPV) or injectable poliovirus vaccine (IPV) at 6 and 10 weeks or at 6, 10 and 14 weeks of age (2001–2004), a phase III efficacy study (2005–2009); and a safety and immunogenicity study in HIV infected infants (2005–2008). The results demonstrated that Rotarix® is well tolerated, safe and immunogenic when co-administered with OPV and other routine EPI vaccines [66,67]. The results further showed no interference of Rotarix® with OPV [66,67]. The Rotarix® efficacy studies have shown an overall protective efficacy of 61.2% in preventing severe rotavirus diarrhoea in South Africa with an efficacy of 76.9% [59]. The efficacy results further indicated that the vaccine could prevent five cases of severe rotavirus disease per 100 infant-years [59]. Finally, Rotarix® has shown to be well-tolerated and immunogenic, with no serious reactogenicity profile in HIV-infected infants; all solicited and unsolicited symptoms were similar in the vaccine and placebo groups [68].

7.4. Scheduling of rotavirus vaccine within EPI-SA

Based on this data and the WHO global recommendation, South Africa introduced Rotarix® into routine childhood national immunisation programme in August 2009 (Fig. 3). The recommended vaccination is a two-dose schedule, administered orally at 6 and 14 weeks of age along with other EPI antigens. To date, more than 3 million doses of Rotarix® had been distributed nationally, although the uptake varies from province to province. Rotavirus vaccination coverage has increased rapidly since its introduction in 2009. By 2010, 67% of less than one year-olds had received a complete 2-dose series of Rotarix®, with 80% of the same cohort having received at least one dose. The coverage rate appears to be on track to exceed this figure in 2011.

7.5. Preliminary analysis of the vaccine impact on the burden of rotavirus infection

Large post-marketing surveillance studies at 5 sentinel sites in three provinces are underway to measure the rotavirus vaccine impact as part of the national surveillance efforts coordinated by the National Institute for Communicable Diseases, a division of the National Health Laboratory Services in Johannesburg. These include Mpumalanga (Mapulaneng and Matikwana Hospitals), Gauteng (Dr George Mukhari and Chris Hani Baragwanath Hospitals) and KwaZulu Natal (Edendale Hospital). Of the 5 sentinel sites, Dr George Mukhari Hospital, located at University of Limpopo Medunsa Campus, has extensive epidemiological data going back to 1982, but systematic sampling for rotavirus BOD surveillance was only initiated in 2003 [9]. Thus, this sentinel site provides an opportunity to measure the preliminary impact of rotavirus vaccination since its introduction into EPI-SA (Fig. 3).

Four trends are evident in the first two rotavirus seasons after the introduction of the vaccine compared to the rotavirus epidemiological trends observed since 2003. First, comparing pre-vaccination (2003–2009) and post vaccination (2010–2011) period, the onset of rotavirus season appears to be delayed by 8 weeks. During the pre-vaccination period, the onset of rotavirus season observed was in April, week 13 and the season lasted for nearly 17 weeks (weeks 13 and 30), whereas in post-vaccination period the onset of rotavirus season was delayed and shifted to week 21 in May, and the average duration of the rotavirus season was between week 21 and 37 (May and September). Second, the rotavirus peaks in the winter season were not as pronounced as the pre-vaccination era. The highest seasonal peak of rotavirus infection during the pre-vaccination seasons was 104/133 cases in 2006, while the highest peak in number of cases was 26/41 in 2010, just over a year after vaccine introduction. Third, the impact of rotavirus vaccination was assessed by comparing the data from 2008 to 2009 (pre-vaccination) and 2010 to 2011 (post vaccination) period, introduction of rotavirus vaccination was associated with substantial reduction in severe gastroenteritis (i.e. 51% reduction) requiring hospitalisation among children less than 5 years of age, translating into reduction in both direct and indirect medical costs. Last, there was substantial decline in gastroenteritis associated with rotavirus infection (i.e. 67%) among children aged 5 years. The post-marketing surveillance studies are still ongoing and the full report from all five sentinel sites will be published in the near future. The post marketing surveillance studies for rotavirus vaccination in the US and Europe also showed a delay in the seasonal peak of rotavirus and significant reduction in the incidence.
of rotavirus gastroenteritis in children younger than 2 years of age [69,70].

8. Conclusion

The introduction of rotavirus vaccine in South Africa is one of the greatest public health achievements. Childhood immunisation programmes against different infectious diseases have generally resulted in a decline in disease morbidity and mortality. It is hoped that there will be a significant decrease in rotavirus burden of disease in the coming years in South Africa. Introduction of the rotavirus vaccine into EPI-SA will contribute to a reduction in all diarrhoeal deaths, mortality related to rotavirus diarrhoea, diarrhoea related hospitalisations and high direct and indirect medical costs of rotavirus disease. This experience will most probably be shared by other African countries as rotavirus vaccine introduction in national immunisation programmes deepens in the region.

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Review

Introduction of pneumococcal conjugate vaccine into the public immunization program in South Africa: Translating research into policy

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Abstract

In April 2009, South Africa was the first African country to introduce pneumococcal polysaccharide–protein conjugate vaccine (PCV) into its public immunization program. This review summarizes studies on pneumococcal epidemiology and PCV undertaken in South Africa, which contributed to the process of advocating for the inclusion of PCV into the public immunization program.

Surveillance prior to the introduction of 7-valent PCV (PCV-7) indicated that 70\% (418/593) of invasive pneumococcal disease (IPD) in infants, the age-group at highest risk of IPD, was attributable to PCV-7 serotypes. Furthermore, 65\% of all IPD in children under-5 years was associated with underlying HIV infection.

Initial immunogenicity studies reported that PCV vaccination of antiretroviral-naïve HIV-infected children was associated with lower geometric mean antibody concentrations and proportion with a serotype-specific antibody concentration above the putative threshold (≥0.35 μg/ml) of protection for IPD for some of the serotypes. The functionality of antibody induced by PCV in HIV-infected infants was inferior to that of HIV-uninfected infants.

Vaccine efficacy of 9-valent PCV in a trial from South Africa reported an 83\% reduction of vaccine-serotype IPD in HIV-uninfected children in the first two years of life, with protection persisting thereafter. However, vaccine efficacy against vaccine-serotype IPD declined from 65\% at 2.3 years of age to 39\% by six years of age in antiretroviral-naïve HIV-infected children.

Based on the observation that a two-dose primary series of PCV during infancy resulted in similar immunogenicity compared to a three-dose schedule, as well as similar impact on nasopharyngeal colonization and effectiveness against IPD in HIV-uninfected children, the South African immunization program adopted a two-dose primary series with a booster dose at 9 months of age. This schedule was largely premised on containing the cost of vaccine introduction, whilst including a booster dose of PCV to assist in prolonging the duration of protection in HIV-infected children.

1. Background

In April 2009, South Africa was the first African country to introduce pneumococcal polysaccharide–protein conjugate vaccine (PCV) into its public immunization program. South Africa, a upper-middle income country, does not qualify for donor support from the Global Alliance for Vaccines and Immunisation (GAVI). Nevertheless, the South African government decided to introduce PCV into the public immunization program allowing access to this potentially life-saving vaccine to an estimated annual birth cohort of 1.2 million children. The introduction of PCV at US$ 25 per dose into the immunization program led to an approximate quadrupling in the direct cost of vaccines procured by the State for use in the public immunization program. Prior to this, the routine immunization programme had included a pentavalent vaccine containing diphtheria and tetanus toxoids, acellular pertussis, Hib-tetanus toxoid and inactivated polio (DTaP–Hib–IPV) and hepatitis B vaccine at 6 (last dose of oral trivalent polio also given), 10 and 14 weeks of age, followed by measles vaccine at 9 and 15–18 months of age.

The introduction of PCV into the South African immunization program followed a recommendation to the Ministry of Health, by the ministerial-appointed National Advisory Group for Immunisation (NAGI) in South Africa [1]. The recommendation by NAGI...
was for South Africa to introduce PCV at 6 weeks, 14 weeks and 9 months dosing schedule. The rational for introducing the vaccine and adopting this schedule instead of a three-dose primary series as then recommended by WHO [2], was based on a series of studies on pneumococcal disease epidemiology and on the immunogenicity and efficacy of PCV in South Africa during the preceding 10–15 years.

The aim of this manuscript is to review studies on pneumococcal epidemiology and PCV undertaken in South Africa over the past two decades which contributed to the process of advocating for the inclusion of PCV into the public immunization program.

2. Pneumococcal disease and HIV infection

Consistent among studies undertaken in South Africa over the past two decades has been the impact of the HIV epidemic on the increased incidence of invasive pneumococcal disease, including pneumococcal bacteraemia and meningitis [3–6]. Although less than five percent of the South African birth cohort during the 2000s were HIV-infected, the incidence (per 100,000) of IPD in HIV-infected children less than two years (3036) was observed to be 42-fold greater compared to HIV-uninfected children [4]. Consequently, almost two-thirds of all childhood IPD episodes in South Africa occurred in HIV-infected children in the 1990s up until mid-2000s [3,4]. Additional effects of the HIV epidemic on the epidemiology of IPD included that HIV-infected children were more likely to develop IPD episodes which were associated with reduced antibiotic susceptibility, including a higher prevalence of multiple-drug resistance (24% vs. 6% in HIV-uninfected children) [4]. Furthermore, whereas the majority of IPD in otherwise healthy HIV-uninfected children occurred within the first two years of life, the risk for IPD persisted beyond this period in HIV-infected children [4,5]. In addition, case-fatality ratios were higher in HIV-infected compared with uninfected children for pneumococcal meningitis (36–38% vs. 12–21%) [4,7], and similar trends were observed in some studies for bacteremic pneumococcal pneumonia (18.2% vs. 10.5%) [4].

HIV-infected children not receiving antiretroviral treatment (ART) were also identified to be at 9-fold increased risk of hospitalization for all-cause pneumonia [5]. In the absence of PCV immunization, Streptococcus pneumoniae was the dominant bacterial isolate from blood in HIV-infected (50% of isolates) and uninfected children (41% of isolates) hospitalized for pneumonia [5].


In addition to hospital-based studies contributing to our understanding of pneumococcal disease in South Africa, an active, nation-wide, laboratory-based surveillance system called GERMS-SA (Group for Enteric, Meningeal and Respiratory disease Surveillance in South Africa) was able to provide additional data to guide prevention strategies. Surveillance was initiated in 1999 [8] and collects data on all cases of laboratory-confirmed IPD diagnosed throughout the country. Although clearly underestimating disease burden, in 2007 in South Africa, pneumococcal meningitis was the dominant cause of reported acute bacterial meningitis in children <1 year old (30.5/100,000 population) followed by meningitis due to Neisseria meningitidis (6.7/100,000) and Haemophilus influenzae (3.9/100,000) [9]. Case-fatality ratios amongst children aged <5 years were high for pneumococcal meningitis (28%, 44/156), the majority caused by 7-valent PCV (PCV-7) serotypes (78%, 281/360).

Using this laboratory-based surveillance system, a reduction in the incidence of IPD was observed from 2003–2004 to 2007–2008 in HIV-infected but not in -uninfected children [10]. This reduction (51%; 95% CI 42–59) among HIV-infected children less than 14 years of age was temporally related to an increase in access to antiretroviral treatment (ART) by HIV-infected children [10]. Notably, this decline occurred independent of introduction of PCV into the public immunization program since 2009. Nevertheless, even in the presence of increased ART access for HIV-infected children, the incidence of IPD in these children remained 21-fold (95% CI 16–28) greater compared with HIV-uninfected children. The relative contribution of HIV to the burden of pneumococcal disease is likely to have diminished further in South Africa since 2009 due to improved ART regimens used in the prevention of mother-to-child transmission programs. Vertical transmission rates of HIV had decreased from 12% in 2008 when mainly intra-partum nevirapine was used, to less than 3% with the current ART regimen recommended for pregnant HIV-infected women and including post-partum nevirapine prophylaxis during the neonatal period (personal correspondence Avy Violari).

Important in the prevention of pneumococcal disease by vaccination is the distribution of serotypes in different settings. Overall, IPD episodes in HIV-infected children were more likely to be due to serogroups commonly associated with pneumococcal colonization; i.e. serogroups 6, 9, 14, 19, 23 (74% vs. 57% in HIV-uninfected children) [4]. Using the national laboratory-based surveillance data, rates of reported disease were highest in children <1 year [11], confirming the age group most at risk of IPD and who should be targeted for national prevention strategies. Serotype 14 (a vaccine serotype) was the commonest serotype in this group. PCV-7 was estimated to potentially prevent 70% (418/593) of IPD in infants if the 6B antigen was considered to cross protect against serotype 6A [11]. In addition, 90% of penicillin non-susceptible disease in children <1 year was due to PCV-7 serotypes including serotype 6A. PCV-10 and PCV-13 increased coverage for all IPD in infants to ~75% and ~85%, respectively. The percentage of isolates that were multiple-drug resistant increased from 16% in 2003 to 20% in 2008 (P<0.001) [12]. The majority of these strains were vaccine serotypes. The risk factors associated with multidrug resistance included age <1 year (adjusted odds ratio [AOR], 2.1; 95% CI 1.8–2.4) and HIV co-infection (AOR, 1.4; 95% CI 1.2–1.7).

4. Immunogenicity of PCV in South African children

Since 1996, a series of studies were conducted in South Africa involving an investigational 9-valent PCV (PCV-9) which included all the serotypes included in PCV-7 (Prevenar®, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; as well as serotypes 1 and 5. Immunogenicity was evaluated in infants immunized at 6, 10 and 14 weeks of age; including following each dose of vaccine [13,14], and following a booster dose [15]. Although the initial immunogenicity study did not screen for HIV infection status in the children, it was imputed that less than 4.5% of the 500 enrolled children may have been HIV infected based on 18% HIV sero-positivity prevalence in pregnant women at the time and vertical transmission rates of HIV being 26% in the absence of ART [16].

The immune responses one-month after the third of the primary series of PCV-9 in the initial study, confirmed the immunogenicity of PCV-9 for all serotypes. In addition, the serotype-specific geometric mean antibody concentrations (GMC) (range 2.73 μg/ml for serotype 23F to 6.18 μg/ml for serotype 5) observed in African children were greater than that observed in studies on PCV-7 in European and North American children [13,14,17,18]. The initial study on PCV immunogenicity in South Africa also reported that >92% of the children had antibody concentrations of >0.5 μg/ml measured by an ELISA assay not incorporating the 22F adsorption step [14]. This threshold would, however, have provided a conservative estimate as to the proportion of children with
serotype-specific antibody concentration of $\geq 0.35 \mu g/mL$ (using the 22F adsorbed ELISA assay), which was subsequently proposed as a putative measure of protection against IPD at a community level [19].

The immune response following each of the three doses of PCV indicated significant serotype-specific antibody production being induced following the first dose of PCV and increase in GMCs after each subsequent dose of PCV. The difference in fold increase in GMCs following the third PCV dose was, however, less marked than after the second PCV dose. In addition, greater-fold increase was observed following the second PCV dose compared with after the first PCV dose [14]. Similarly, there were fewer differences in the proportion of children with serotype-specific antibody concentration of $>0.5 \mu g/mL$ following the third compared to after the second dose of PCV, with $>75\%$ of all children having antibody concentrations to each of the 9 serotypes after two doses of PCV [14]. Whereas there was a one-month interval between the primary series of PCV in this study [14], a subsequent study from the United Kingdom reported that immune response during a primary series of two doses of PCV during infancy was enhanced if there was greater interval between the two doses; i.e. eight weeks rather than four weeks apart [20]. These data were used in part in deciding to include PCV as a two-dose primary series given at 6 and 14 weeks of age in the South African immunization program.

The initial South African immunogenicity study also evaluated the persistence of anti-polysaccharide antibody in the second year of life and immune responses to either a booster dose of PCV or 23-valent pneumococcal polysaccharide vaccine (PPV) at 18 months of age [15]. Higher antibody concentrations persisted in previous PCV-9 recipients at 9 and 18 months of age compared with placebo recipients.

The immune response to PCV-9 was also evaluated in ART-naïve HIV-infected children. In general, GMCs following the primary series of three doses of PCV-9 were lower in HIV-infected compared with HIV-uninfected children, although only significantly so for serotypes 1 and 18C [21]. Among HIV-infected children, those with CDC clinical stage C HIV/AIDS illness had lower GMCs compared with children who were asymptomatic or only mildly symptomatic for HIV disease (Category N or A). In addition, a lower proportion of HIV-infected children had serotype-specific antibody $\geq 0.35 \mu g/mL$ for four (serotypes 1, 5, 18C and 23F) of the nine serotypes compared with HIV-uninfected children. The proportion of children with serotype-specific antibody $\geq 0.35 \mu g/mL$ ranged from 80% (serotype 6B) to $>95\%$ for the other serotypes in HIV-uninfected children, compared with 62% (serotype 6B) to 82–95% for other serotypes in HIV-infected children.

An additional measure of PCV immunogenicity, that is suggested to be more predictive of protection against IPD, is the presence of antibody-killing activity measured by opsonophagocytic assay activity (OPA). HIV-infected children were observed to be less likely than HIV-uninfected children to have detectable killing activity (titer of $\geq 8$) on OPA for all three serotypes evaluated, i.e. serotypes 6B (78% vs. 96%), 19F (46% vs. 91%) and 23F (57% vs. 93%) [21]. In addition, the concentration of antibody required for 50% killing activity on the OPA was significantly higher for all serotypes in HIV-infected compared with -uninfected children. This suggests that antibody concentration required to protect against IPD may be higher in HIV-infected children, and that OPA assays may be a more useful measure as a putative measure of protection in these immune-compromised children [21].

A subsequent study in South Africa indicated that persistence of serotype-specific antibody was significantly lower for six of the serotypes evaluated 5.3 years after vaccination [22]. In addition, a lower proportion of HIV-infected children had serotype-specific antibody concentration of $\geq 0.35 \mu g/mL$ for all seven evaluated serotypes (excluded 1 and 5) which ranged from 60% for serotype 9V to 78% for serotype 6B, compared with $>98\%$ for all serotypes in HIV-uninfected children. The GMCs following a booster dose of PCV at 5.3 years after the primary series of three doses of PCV in HIV-infected children were similar in magnitude compared to the response to a single dose of PCV among HIV-infected children who had previously received placebo. This indicated either failure to induce membro B-lymphocytes following the primary series of PCV, or the subsequent loss of anamnestic response among ART-naïve HIV-infected children whose immune systems deteriorated progressively [22].

In addition, a single dose of PCV-7 in previously unvaccinated children during the 5th–6th year of life was associated with markedly lower GMCs in HIV-infected compared with -uninfected children for all seven serotypes. Furthermore, the proportion of HIV-infected children with antibody concentrations $\geq 0.35 \mu g/mL$ ranged between 38% (serotype 23F) and 60% for other serotypes (except 79% for 19F), compared with $>94\%$ for all serotypes (except 78% for 6B) in HIV-uninfected children following the single dose of PCV. These data indicated that HIV-infected children may require booster doses of PCV to sustain their protection against IPD, as well as that multiple doses of PCV may be required when vaccinating HIV-infected children for the first time beyond the infancy period.

5. Efficacy of PCV against nasopharyngeal colonization in South African infants

Nasopharyngeal colonization by pneumococcus, although possibly innocuous in the majority of colonized children, is nevertheless a pre-requisite for the development of mucosal and invasive pneumococcal disease. The risk of developing pneumococcal disease is greatest within two months of becoming colonized by a new serotype [23]. An initial study in The Gambia using an investigational pentavalent pneumococcal conjugate vaccine was the first to report a reduced risk of nasopharyngeal acquisition of the vaccine serotypes following immunization [24]. In South Africa, this was further corroborated in a study by Mbelle et al. [13] in which 50% reduction in colonization by the vaccine serotypes was reported at 9 months of age. There was, however, a 30% increase in nasopharyngeal colonization by the non-vaccine serotypes and consequently PCV vaccination did not change the overall prevalence of pneumococcal colonization. In addition, notably, PCV vaccination was associated with a reduction in colonization by pneumococcal strains associated with penicillin-resistance (21% vs. 41%) and cotrimoxazole-resistance (23% vs. 35%). The effect of PCV on reducing the risk of vaccine-serotype nasopharyngeal acquisition has since been corroborated by a number of studies including one in The Netherlands which reported a similar effect using a two-versus a three-dose primary series of PCV followed by a booster dose in the 2nd year of life [25].

Childhood PCV immunization has been associated with a temporal reduction in vaccine-serotype IPD and all-cause pneumonia in age-groups not targeted for vaccination, including the elderly and HIV-infected adults [26–30]. This indirect effect, due to decreased pneumococcal acquisition in vaccinated children resulting in decreased transmission overall, may also contribute to the observation that the effectiveness of PCV against all-cause pneumonia in USA among the age-group targeted for vaccination [22–45%], post-introduction of vaccine into immunization programs [27,29,31], has exceeded the expectations based on the efficacy trial in Northern California (5%) [18].

6. Efficacy of PCV against IPD in South African children

A phase 3 study, which enrolled 39,836 children from March 1998 to October 2000, with follow-up being extended until October
ing PCV efficacy, it undermines the public health potential of PCV.

Following a mean 2.3 years of follow-up, vaccine efficacy against vaccine-serotype IPD was 83% (95% CI 39–97) in HIV-uninfected children compared with 65% (95% CI 24–86) in HIV-infected children [32]. Despite the lower vaccine efficacy in HIV-infected children, the absolute burden of vaccine-serotype IPD prevented in HIV-infected children (570 per 100,000 child years) was 18-fold greater compared with HIV-uninfected children (32 per 100,000 child years). Whereas vaccine efficacy against vaccine-serotype IPD remained relatively unchanged in HIV-uninfected children (78%; 95% CI 34–93) following a mean follow-up of 6.2 years, there was a decline in efficacy in HIV-infected children (39%; 95% CI 0–65) [22]. This indicated loss of protection in the absence of a booster dose of PCV and was corroborated by the poor long-term immunogenicity data in ART-naïve HIV-infected children [22].

A meta-analysis [33] of vaccine efficacy against IPD due to the seven serotypes included in PCV-7, although reporting homogeneity in efficacy between studies, nevertheless indicated lower point efficacy estimates against vaccine-serotype IPD in both African studies [32,34] (77%) compared with that observed in North American children (94%) [18] (Fig. 1). PCV-9 efficacy was also evaluated against IPD due to any serotype. Inclusive of the extended follow-up period, vaccine efficacy in South African HIV-infected children was surprisingly greater in HIV-infected (46.1%) compared with HIV-uninfected children (35.0%; P < 0.0001). This was primarily driven by protection against serotype 6A disease, due to cross-protection by the inclusion of serotype 6B in the vaccine. Serotype 6A singularly contributed to 27% of all IPD cases in the HIV-infected placebo group; and serotype-specific protection was observed in HIV-infected children even 5 years after vaccination. In addition, despite the waning immunity against vaccine-serotype IPD in HIV-infected children, the overall burden of IPD prevented by PCV-9 was 59.2 (95% CI 43.0–81.6) fold greater in HIV-infected compared with HIV-uninfected children (2250 vs. 38 IPD cases prevented per 100,000 children vaccinated, respectively).

Notably, in HIV-uninfected children, the absolute overall reduction in IPD was almost halved (38 per 100,000) relative to the reduction for vaccine type IPD (75 per 100,000), primarily due to a non-significant increase (75%; 95% CI −17.8 to 94.7; P = 0.11) in IPD due to non-vaccine serotypes (mainly serotype 19A). The study was however not powered to determine whether this increase in non-vaccine serotype IPD was significant. An increase (27%) in non-vaccine serotype IPD was also observed in HIV-infected children, although this increase in incidence was only 10% of the decline in vaccine-serotype IPD among these children. Contrary to the meta-analysis on vaccine-serotype IPD, significant heterogeneity was observed between studies in efficacy against overall IPD. This ranged in vaccine efficacy estimates in HIV-uninfected children of 35–45% in the two studies from Africa compared with 89% in USA. The lower efficacy against overall IPD in African studies [32,34] compared with studies from USA [18] may have been due to the greater diversity of serotypes associated with IPD in African compared with North American children, as well as possibly greater, albeit not statistically significant, increase in non-vaccine serotype IPD.

7. Efficacy of PCV against pneumonia in South African children

Although IPD provides a useful specific outcome for measuring PCV efficacy, it undermines the public health potential of PCV. In particular, IPD accounts for less than 10% of the annual 14 million episodes of severe disease and 847,000 deaths attributed to pneumococci globally [35]. The major clinical manifestation of severe and fatal pneumococcal disease is pneumonia. However, a major challenge in evaluating the effect of PCV against pneumococcal pneumonia relates to the lack of sensitive assays to make an etiologic specific diagnosis causing pneumonia, and particularly relevant to bacterial pneumonia. Although lung aspirates allow for increasing the yield of making an etiologic specific diagnosis, these are rarely undertaken and are also biased by largely being limited to pneumonia episodes associated with alveolar consolidation in the periphery of the right lung. Hence, the spectrum of pathogens identified through lung aspirates may not be fully representational of all cases of pneumonia. To overcome this challenge in part, as well as to provide a standardized outcome measure against which efficacy trials could be compared, a working-group under the auspices of the WHO recommended a radiologic outcome to be used when measuring the efficacy of PCV against pneumonia [36]. This outcome, commonly referred to as “radiological-confirmed pneumonia (RCP)” was subsequently reported on in studies which evaluated the efficacy of PCV against pneumonia [32,34,37,38]. In addition, many studies also reported on the broader clinical syndrome of clinically diagnosed pneumonia.

In South Africa, the efficacy of PCV-9 against RCP following an average of 2.3 years of follow-up was 20% (95% CI 3–35) in HIV-uninfected and 13% (95% CI 7–28) in HIV-infected children [32]. Despite the lower point-efficacy estimate in HIV-infected children, the vaccine-preventable burden (per 100,000 vaccinated children) of hospitalized RCP was nine-fold greater in HIV-infected (909) compared with -uninfected children (100). Furthermore, the burden (per 100,000 children) of vaccine-serotype bacteremic pneumococcal pneumonia prevented was 38-fold greater in HIV-infected children (344) compared with -uninfected children (9). The evaluation of PCV in the South African setting was also used as a tool with which to probe the clinical presentation and pathogenesis of pneumonia in HIV-infected and -uninfected children. Included in this was the recognition, that whilst only 3% of all pneumococcal pneumonia that was prevented in HIV-uninfected children were associated with bacteremia, this proportion was much greater in HIV-infected children (18%) [16].

Post hoc analysis of the South African efficacy trial also probed the role of pneumococcus in the broader spectrum of pneumonia. This was especially pertinent as radiologic-confirmed pneumonia in placebo-recipients only accounted for 19.2% of all hospitalized pneumonia episodes in South Africa [16], as well as only 16.7% of episodes in The Gambian study on PCV-9 [34]. Although vaccine efficacy was notably lower for the less specific outcome measure being evaluated in South African children, the public health relevance of examining vaccine efficacy against the broader syndrome of clinical pneumonia was noted. In particular, less specific endpoints with lower point-efficacy estimates detected a larger burden of pneumococcal pneumonia which was prevented by PCV compared with those endpoints with outcomes which were more specific for pneumococcal pneumonia (Fig. 2) [16].

8. Recommendation of NAGI on PCV dosing schedule in South Africa

The high cost of introducing PCV into South Africa, which is non-eligible for GAVI support, required interrogation of the epidemiology and existing evidence on PCV to inform decision-making as to what schedule PCV should be used in the immunization program. Limited funds to support the program precluded using a three-dose primary series with booster dose (i.e. 3 + 1 schedule). However, the lack of sustained protection against IPD in
HIV-infected children who contributed to more than two-thirds of IPD in South Africa, indicated a need for a booster dose of vaccine.

Based on the observation that a two-dose primary series of PCV during infancy resulted in similar immunogenicity compared to a three-dose schedule [14,20] as well as similar impact on nasopharyngeal colonization and effectiveness against IPD in HIV-uninfected children [25,39], NAGI recommended that the South African immunization program adopt a two-dose primary series with a booster dose at 9 months of age. Providing the booster dose of PCV at 9 months of age optimizes the number of children who are likely to receive the booster dose. In particular, there is an attrition of children who are brought for their routine immunizations at 9 months (95%) compared with 18 months (83%), according to official country estimates for 2010 [40].

9. Main questions needing to be addressed with introduction of PCV in South Africa/Africa

Despite the broad repertoire of research undertaken on pneumococcal disease and PCV over the past two decades in South Africa, a number of questions remain. These include the immunogenicity of the novel 2 + 1 dose, in both HIV-infected and -uninfected children. In addition, with increased access to ART in management of HIV-infected children, the persistence of antibody, anamnestic responses and sustainability of protection against IPD in HIV-infected children on anti-retroviral treatment needs evaluation.

The effectiveness of the novel 2 + 1 schedule used, and in particular in protecting against IPD in HIV-infected children, is currently being evaluated in South Africa. Furthermore, there are concerns that a two-dose primary series may be less effective than a three-dose primary series against pneumonia [41]. Considering that >90% of severe pneumococcal disease morbidity and mortality relates to pneumonia [35], the effectiveness of the 2 + 1 schedule, in both HIV-infected and -uninfected African children requires confirmation and is also currently being studied in South Africa. This will be supported by an ecological time-series analysis on the impact of PCV introduction on all-cause pneumonia hospitalization at a sentinel hospital site in South Africa.

Whereas the above studies were initiated at the time when 7-valent PCV was used, the transition from PCV-7 to 13-valent PCV as of May 2011 will likely need to be extended to include evaluating the effectiveness of the immunization program against the dominant IPD-causing serotypes, i.e. 1 and 19A, which contributed to a greater proportion of IPD post PCV-7 introduction.

Other studies also currently underway include the national laboratory-based surveillance system monitoring trends in incidence of IPD, including stratification by HIV, across various age-groups to delineate the direct and indirect impact of childhood PCV immunization on vaccine-serotype IPD. The IPD surveillance study examining the effect of infant PCV immunization, in the absence of a childhood catch-up campaign as was the case in South Africa, on indirect protection is also being supplemented by an ecological study on the effect of infant PCV immunization on the epidemiology of vaccine and non-vaccine serotype nasopharyngeal colonization in both rural and urban areas, across

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**Fig. 1.** Meta-analysis: efficacy in randomized-controlled trials of pneumococcal conjugate vaccine (PCV) against invasive pneumococcal disease due to serotypes included in 7-valent PCV among HIV-uninfected children [33].

Adapted from reference number [33].

**Fig. 2.** Inverse relationship between vaccine efficacy and vaccine attributable reduction (VAR) (per 100,000 children) in HIV-uninfected children [16].

PCV=pneumococcal conjugate vaccine; WHO=World Health Organization; CXR=chest X-ray.
The IPD surveillance system would also provide vital information as to the temporal trends in non-vaccine serotype IPD post-introduction of PCV-7 to help understand the public-health relevance of serotype-replacement disease in South Africa. Archiving of the pneumococcal isolates will also provide an opportunity of evaluating the molecular basis of any excessive replacement disease which may be observed in South Africa.

Conflict of interest statement

SAM has participated in speakers' bureau (GlaxoSmitKline and Pfizer), received grant funds (GlaxoSmithKline, Pfizer and sanofi-aventis) and honoraria (GSK, Pfizer, sanofi-aventis, MERCK). AvG has received grant funding from GlaxoSmithKline, Pfizer and sanofi-aventis.

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References


Review

Introducing human papillomavirus vaccines into the health system in South Africa

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A B S T R A C T

South Africa has a high incidence of cervical cancer, with an age-standardised rate of approximately 27 per 100,000. In 2000, South Africa launched a national screening programme for cervical cancer prevention, offering three Papanicolaou smears per lifetime starting after the age of 30 with 10-year intervals. However, in the public sector, this national screening programme has not been implemented widely. Vaccination would offer the best primary prevention. Currently there are two HPV vaccines registered in South Africa: the bivalent vaccine Cervarix™, containing VLP antigens for oncogenic HPV types 16 and 18; and the quadrivalent vaccine Gardasil™, containing VLP antigens for HPV types 16 and 18, as well as non-oncogenic HPV types 6 and 11, which are the most common types causing genital warts. The vaccines are recommended for prophylactic use, and should ideally be given before exposure to HPV, which is before sexual debut, to girls aged 11–12 years. Possible routes for delivering the HPV vaccine could be either the routine EPI programme at the age of 12 years when dT is being administered, or through the school system, e.g. to girls attending grade 5 or 6.

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1. Introduction

South Africa is classified as an upper middle-income country by the World Bank [1]. The Gross Domestic Product is around $5800 per capita but the distribution is unequal. The rate of poverty (the percentage of the population living below the national poverty line as defined by the World Bank) declined significantly over the last few years but still stands at 23%. South Africa spends 3% of its GDP and just over 15% of government expenditure on healthcare. When compared to low- and middle-income countries the level of total health expenditure is relatively high. This high spending does not translate into a healthy population [2]. Human development challenges are enormous and there is a low life-expectancy of only 51 years.

Accurate data on causes of death are not always available and cancer statistics are often lacking and inaccurate [3]. Cancer prevention as a health priority has to compete with communicable diseases like HIV and tuberculosis. Partly related to the poor quality of cancer preventative services there is a high incidence of cervical cancer in South Africa.

South Africa has a two tier medical system with considerable overlap. Approximately 20–25% of the population is covered by private medical insurance and makes use of modern, generally well-resourced, private sector facilities. Approximately 75–80% of the population depends on the state sponsored health-care of which the quality is quite variable according to geographical areas. A small but significant part of the population will access primary care in the private sector but will use the public sector for hospitalisation and specialised services.

2. The burden of HPV associated disease

Persistent HPV infection with an oncogenic strain of HPV is a necessary risk factor for the development of invasive cervical cancer [4]. The most important oncogenic viruses seem to be similar in many different geographical areas and HPV16, 18 and 33 were identified in the majority of cervical cancer biopsies from South Africa [5]. Oncogenic strains of HPV have the ability to integrate viral DNA into the human genome. The onco-proteins E6 and E7 deactivate important processes associated with tumour suppressor genes like p53 and pRb gene functions. HPV is highly infectious and "most sexually active people will get HPV at some time in their lives" [6]. This ubiquitous infection does not cause disease in all the infected individuals and certain processes make individuals more susceptible to the development of pre-malignant and malignant disease. Because
HPV is almost exclusively an epithelial disease, the virus is poorly presented to the adaptive immune system which is important for induction of long term immunity. Most natural infections of HPV do not cause significant immunoglobulin responses and therefore the immune response after natural infections is not very pronounced [7].

After initial exposure to HPV there is an incubation period of between 1 and 8 months after which the first HPV-related lesions might appear. There is active growth of the virus for a period of between 3 and 6 months but usually there are host-immune responses that will, in most cases, clear the infection by about 9 months. A large percentage of the population will have sustained clinical remission but a small proportion will develop chronic infection and become HPV-DNA positive on repeated testing. These are the individuals that will be at highest risk for the development of pre-malignant conditions and later invasive cancer [7]. We now know that changes in cells due to HPV infection of the cervix is the first step in a series of slow changes that can lead to cancer years later.

The age-standardised incidence rate of cervical cancer in Southern Africa is approximately 27 per 100,000 [8]. There is a significant difference in reported rates between black (42.1) and white women (14.5) which may be partly related to unequal access to healthcare, differences in socio-economic status and exposure to HPV and HIV infection [9]. Not only is the incidence of cervical cancer unacceptably high, but also most cases of invasive carcinoma present late with a high case-fatality.

Other malignant diseases associated with human papillomavirus infection like oesophageal tumours, head and neck tumours and invasive vulva carcinoma are not uncommon in South Africa [10]. Cancer of the penis represents less than 0.5% of cancers in men [11]. There is geographical correlation between the incidence of cancer of the penis and cervix, and concordance of these two cancers in married couples, which suggests that HPV is the common aetiology.

Despite the fact that screening services are inadequately developed, many women still undergo cervical excision procedures for premalignant conditions. In this population premature delivery is already an important health problem [12]. Additionally, it has been reported that treatment for cervical intra-epithelial neoplasia (CIN) significantly increases the risk for preterm delivery and low birthweight infants [13,14]. The risk for premature delivery may be higher after cold knife conisation when compared to loop excision and laser procedures [15].

Non-oncogenic HPV (mainly types 6 and 11) is the cause of serious benign conditions such as recurrent juvenile papillomatosis and condylomata acuminata (genital warts) [16]. External genital disease including condylomata acuminata (and vulva intra-epithelial neoplasia) often presents as a clinical dilemma; particularly in the HIV-infected population. However in clinical practice it is abundantly clear that genital warts is a common clinical problem that cause serious morbidity and cost to the health system. Massive condylomata acuminata will not infrequently be diagnosed during pregnancy or in HIV infected individuals.

3. Screening for cervical cancer

3.1. Cytology

The South African National policy for cervical cancer prevention was launched in 2000. The screening programme offers three Papanicolaou smears per lifetime starting after the age of 30 at 10-year intervals [17]. This policy is based on a mathematical model that predicts a reduction in cervical cancer incidence in excess of 60% if the policy is universally introduced. If a low-grade abnormality is found the cytology smear is repeated after 12 months. Referral threshold for colposcopy include two consecutive low-grade lesions, one high-grade lesion or a macroscopic lesion suspicious of cancer. For women with HIV infection, the clinical guidelines for the management of HIV and AIDS in adults and adolescents advises one cervical cytology at diagnosis of HIV and then every 3 years if normal regardless of antiretroviral treatment status [18].

In certain parts of South Africa (particularly in the private sector) opportunistic screening with regular Pap smears has resulted in a significant drop in the rate of cervical cancer [19]. However, in the state sector, the national cytology screening programme has not been implemented widely. Some provinces in South Africa have fairly well-developed cytology screening services but overall there is poor uptake of secondary prevention services for cancer. In those women identified with abnormal cytology there is a significant loss to follow up after the initial screening test [20].

3.2. Human papillomavirus testing

Human papillomavirus testing has been extensively investigated as an alternative to cervical cytology for screening. The high sensitivity to detect precursor lesions may make HPV testing more suitable than cytology in an once-in-a-lifetime programme or a programme with long screening intervals. HPV testing as a primary screening tool has been compared to various other methods in the South African setting [21]. Certain subgroups of the population are not suited to HPV screening due to a very high prevalence of HPV. This includes women below the age of 30 years where HPV detection is mostly transient [21]. In immune compromised women the incidence of HPV is also high but the high negative predictive value of HPV DNA testing may be useful as a triage method. Cost effectiveness calculations from South Africa indicate that HPV testing to screen for cervical cancer may be a cost-effective strategy although analyses are affected significantly by the specific protocol and situation [22].

3.3. Visual Inspection

In certain rural areas of South Africa visual inspection with acetic acid (VIA) is the preferred option for secondary prevention.

4. The role of Human Immune Deficiency Virus (HIV) co-infection

Southern Africa has the highest incidence of HIV-infected individuals anywhere. Despite that the biggest anti-retroviral programme in the world has been rolled out over the last few years, the life expectancy of South Africans has fallen drastically largely due to an excess mortality associated with AIDS related illnesses. One of the recognised HIV associated diseases is cervical cancer and its precursors. Unpublished data collected at the first author’s institution confirms the fact that HIV infected individuals have significantly more abnormalities on cervical cytology, are far more likely to be HPV positive and test positive for many HPV types, have a higher failure after excisional treatment for pre-cancer lesions and present much younger with invasive carcinoma. These findings are confirmed by publications from other authors [23–25].

There are an increasing number of reports supporting a possible relationship between HPV infection and the risk for HIV acquisition [26,27]. HIV and genital HPV infection share similar risk factors. It seems that the presence of HPV infection actually increases the risk for HIV acquisition and transmission and the biological plausibility of this phenomenon is explored in recent publications [28,29].
effective HPV prevention strategy may therefore also reduce the risk for HIV infection.

5. Treatment facilities available in Southern Africa

Treatment facilities for invasive cervical cancer are limited. Despite the fact that most cancers are diagnosed quite late, a significant number of women qualify for radical surgery as primary treatment. There are less than 20 registered gynaecological oncologists in the country. Radiotherapy facilities are in high demand and waiting lists for treatment are often unacceptably long. Palliative support is lacking in many parts of the country particularly in rural areas.

6. Primary preventative strategies

HPV vaccines are produced using recombinant technology, whereby the L1 capsid protein is inserted into a host (e.g. yeast or baculovirus). These L1 proteins can self-assemble into empty shells or virus like particles (VLPs) that are similar in size and shape to the HPV virion. VLPs do not contain viral DNA, and are therefore non-infectious and non-oncogenic [30,31].

Currently there are two vaccines registered in South Africa: the bivalent vaccine Cervarix™, containing VLP antigens for HPV types 16 and 18; and the quadrivalent vaccine Gardasil™, containing VLP antigens for HPV types 16 and 18, as well as non-oncogenic HPV types 6 and 11, which are the most common types causing genital warts. VLPs are combined with an immune stimulant, called an adjuvant, which leads to an improved immunoglobulin production.

The bivalent vaccine uses a unique type of adjuvant, ASO4, an adjuvant, which leads to an improved immunoglobulin production. Both vaccines are given as intramuscular injection in a three-dose schedule: 0, 1 and 6 months for the bivalent vaccine; 0, 2 and 6 months for the quadrivalent vaccine [30].

Both vaccines have been studied in large populations and have been found to be safe and well tolerated. Local reactions like pain, swelling and redness can occur and are of short duration. Systemic adverse events could include fever, nausea, dizziness, fatigue, headache and myalgia [32]. The HPV vaccines are also well tolerated in boys [33,34]. It is safe to co-administer the HPV vaccines with other paediatric and adolescent vaccines [30].

6.1. Efficacy

A study that provides recent comprehensive data pertaining to the clinical efficacy of Cervarix™ is the HPV-008 PATRICIA study (the PApilloma TRIal against Cancer In young Adults) [35]. The primary objective of this study was to assess vaccine efficacy against CIN2+ associated with HPV16/18 in women who were sero-negative and DNA negative at baseline and month 6 for the corresponding type. The study was a randomised 1:1, double blind, controlled Phase III trial involving 18,644 young women aged 16–25 years. The interim analysis was reported after a mean follow-up of 14.8 months [32] and the final analysis conducted after a mean follow-up of 34.9 months [35]. A total of 92% of the participants received three doses of the study vaccine.

The final analysis included 3 study cohorts, Total Vaccinated Cohort (TVC), Total Vaccinated Cohort-Naive (TVC-Naive) and According to Protocol Cohort (ATP-E). The TVC-Naive cohort approximated the primary target population for organised vaccination programmes, namely adolescent girls before sexual debut.

The efficacy of the vaccine after 34.9 months in the ATP-E cohort was 92.9% for CIN2+ associated with HPV16/18 in the primary analysis and 98.1% in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types. Within the TVC-Naive cohort the protection against HPV16/18 CIN2+ was 98.4% and against HPV16/18 CIN3+ it was 100% [35]. This study also reported cross-protection against persistent HPV infection and CIN2+ associated with HPV31, HPV33 and HPV45. Vaccination with the bivalent vaccine decreased colposcopy referrals and cervical excision procedures [36].

End of study data obtained after 4 years of the randomised, double-blind PATRICIA trial, showed that the vaccine efficacy in the TVC was considerably less than observed in the TVC-naive. Vaccine efficacy against CIN3+ associated with HPV16/18 was 100% in the TVC-Naive group and 45.7% in the TVC group. When stratified by age in the TVC group, the highest vaccine efficacy was observed in the youngest age group (15–17-year old), and decreased with increasing age (18–20-year old; 21–25-year old) [37]. Vaccine efficacy against all CIN3+ irrespective of HPV type in the lesion and including lesions with no HPV DNA was 93.2% in the TVC-naive, and 45.6% in the TVC.

De Carvalho et al. reported efficacy data of the bivalent vaccine up to 7.3 years after first vaccination [38]. The study was conducted in Brazil and enrolled 433 young women (age 15–25 years) who were sero-negative and DNA-negative in a double-blind, randomised trial. Vaccine efficacy at 94.5% against incident infection remained high up to 7.3 years. Hundred percent vaccine efficacy was observed against 6-month and 12-month persistent infection with HPV16/18, as well as CIN1+ and CIN2+.

The quadrivalent vaccine has been evaluated in 2 phase III randomised placebo controlled clinical trials in women aged 16–26 years: protocol 013 (termed FUTURE 1) and protocol 015 (termed FUTURE II) [39]. In the per-protocol population, the vaccine efficacy was 96% for CIN1, and 99% for condylomata after 4 years of follow-up.

Steben reported the end of study data for the quadrivalent vaccine after 4 years of follow-up of women aged 16–26 years [40]. The vaccine efficacy for HPV16/18 related CIN2/3 was 98%. For women aged 24–45 years, per-protocol vaccine efficacy for any HPV6/11/16/18-related disease was 92%. Efficacy of the quadrivalent vaccine has been shown in adult women aged 24–45 years in a combined analysis of 4 randomised placebo controlled clinical trials [41]: after an average of 3 years of follow-up, vaccine efficacy was 99% in the per protocol study population for the prevention of CIN2/3 and adenocarcinoma in situ. External genital lesions were also significantly reduced in the vaccinated cohort and there was a significant reduction in colposcopy, cervical biopsy and in surgical therapy [42]. In a study among 4065 healthy men 16–26 years of age, the quadrivalent HPV vaccine significantly reduced the incidence of persistent HPV infection and external genital lesions related to HPV6, 11, 16, and 18 [43].

Information on the use of the quadrivalent vaccine in immunocompromised patients is limited to a small study done in 126 children in the United States who were between the ages of 7 and 12 years. Some of these children were on antiretroviral therapy and some were not. Around 99.5% developed antibodies to HPV when vaccinated with the quadrivalent vaccine [44]. A trial on the safety and immunogenicity of the bivalent vaccine in HIV infected females is currently on-going in South Africa [45].

6.2. Immunogenicity/duration of protection

Both the bivalent and the quadrivalent vaccine are highly immunogenic across a wide age-range, but the highest immune responses were observed in young girls aged 9–15 years [32,33,46,47]. Both vaccines induce HPV16 antibody titres several fold higher than after natural infection: these titres remain high for at least 8.4 years for the bivalent vaccine with 100% seropositivity.
maintained and at least 5 years for the quadrivalent vaccine with 98.8% seropositivity maintained [48]. The bivalent vaccine induces sustained antibody titres for HPV18 several fold higher than after natural infection, 8.4 years after initial vaccination with 100% seropositivity maintained. However, for the quadrivalent vaccine, 18 months after first vaccination, the induced antibody titres for HPV18 return to the level of natural infection, with a reduction in seropositivity over time [48]. A minimum protective level of antibodies has not yet been established and despite falling levels of antibodies, protection against detectable disease was demonstrated for the quadrivalent vaccine for more than 5 years.

A strong anamnestic response was induced after administering a fourth dose after 5 years for the quadrivalent vaccine [49] and after 7 years for the bivalent vaccine [50]. These findings would support a long term efficacy of both vaccines.

Einstein compared the immunogenicity of the bivalent with the quadrivalent vaccine. Neutralising antibodies against HPV16 and HPV18 were 3.7 and 7.3-fold higher, respectively for the bivalent vaccine compared to the quadrivalent vaccine in women aged 18–26 years [51]. These differences remained similar in older age groups. This difference in immunogenicity could be due to the different adjuvants used in the bivalent and quadrivalent vaccine [38,52]. A higher immune response may indicate a longer duration of protection against HPV16/18, however, long-term studies are needed to assess the clinical relevance of the observed differences in antibody response [51].

6.3. Cross-protection

Both HPV vaccines protect against other HPV types than just those that are present in the vaccines. HPV31 and HPV45 are responsible for about 10% of cervical cancer worldwide. HPV31 is phylogenetically related to HPV16 and HPV45 is related to HPV18.

The bivalent vaccine showed cross-protection against HPV31 and HPV45 [38,53]. Vaccine efficacy against 6-month persistent infection was 79% for HPV31, and 76% for HPV45 [53]. No cross-protection was observed against HPV52 or HPV58. In addition to cross-protection against HPV31 and HPV45, Paavonen et al. reported also vaccine efficacy of 51.9% against CIN2+ for HPV33 [35]. HPV33 is phylogenetically related to HPV16 and an important HPV type in South Africa. End of study data obtained after 4 years of the randomised, double-blind PATRICIA trial, showed vaccine efficacy against persistent infection and CIN2+ (with or without HPV16/18 co-infection) for HPV31, HPV33, HPV45 and HPV51 [54]. Vaccine efficacy against CIN2+ with or without HPV16/18 co-infection for HPV31 was 87.5% in the ATP-E, 89.4% in the TVC-naïve and 47% in the TVC group. For HPV33, a vaccine efficacy against CIN2+ was observed of 68.3% for the ATP-E, 82.3 for TVC-naïve, and 51.5% for the TVC group. For HPV45, a vaccine efficacy against CIN2+ was observed of 81.9% for the ATP-E, 100% for TVC-naïve, and 90.5% for the TVC group. For HPV51, a vaccine efficacy against CIN2+ was observed of 54.4% for the ATP-E, 70.2 for TVC-naïve, and 50.0% for the TVC group [54].

The quadrivalent vaccine showed cross-protection against HPV31 and HPV33, in subjects who were sero-negative and DNA negative at enrolment. Vaccine efficacy against 6-month persistent infection was 46.2% for HPV31, and 28.7% for HPV33 [55,56]. Vaccine efficacy against CIN2+ or adenocarcinoma in situ was 70% for HPV31 and 24% against HPV33. There was no cross-protection observed against infection and lesions with HPV45 [56].

7. Public health

The vaccines are recommended for prophylactic use, they do not clear an existing infection or disease. In order for the vaccine to be effective in preventing HPV infection, it must be given before exposure to HPV, which is before sexual debut. Studies on the natural history of HPV infection and disease have shown that the peak incidence of HPV infection occurs in most populations within 5–10 years of first sexual experience (age 15–25 years). There may be some differences between countries but in general most authorities recommend that girls around age 11–12 years, just before leaving primary school, may be the most suitable for mass vaccination. The vaccine can however be administered as young as 9 years of age. Catch-up vaccination is considered cost-effective for females aged 13–18 years [57,58].

High vaccine coverage is needed if significant improvement of cervical cancer rates is to be achieved. In many industrialised countries the introduction of the vaccines has been rapid and very well organised. Examples of well-organised vaccination programmes for girls are the National Health Service in the United Kingdom, the Australian government programme and the programme in Belgium [59]. These programmes aim to vaccinate all girls around the age of 12 but for the first few years also include a catch-up group of slightly older adolescents/young women. At present HPV vaccination for males is not recommended, but it could be considered to include them when the vaccines become less expensive [60]. The uptake of these vaccines has been good in developed countries with an acceptance rate of over 70% in both Australia and the United Kingdom [61,62]. In Belgium, vaccination coverage of 83.2% for the third dose was observed [63]. Even in developing countries demonstration projects have been met with local enthusiasm and support and it was found in Uganda that “...people in diverse contexts are supportive of action to address cervical cancer, in spite of concerns and obstacles that will need to be addressed” [64].

Rwanda became the first country in Africa to announce a national prevention programme for cervical cancer that includes HPV vaccination. The programme will aim to vaccinate girls aged 12–15 years and HPV testing for women between 35 and 45 years. This programme has been made possible because of a 3-year donation of 2 million doses of the quadrivalent vaccine and 250,000 HPV screening tests. The vaccine company also agreed to provide Rwanda with a discounted price after 3 years. The price is unknown at present but Rwanda will probably require help from donors to pay for the vaccine [65]. In South Africa Gardasil™ and Cervarix™ are both available in the private sector and are currently being considered for a national vaccination programme. A vaccination programme in South Africa will almost certainly make a significant difference in the cervical pre-cancer and cancer incidence in the future. South Africa has a high rate of infant vaccination and the principles of vaccination are well known to health care professionals and trusted by the general public. The benefit over the medium to long term will likely be substantial in terms of cost of treatment and diagnosis of pre-malignant and malignant cervical disease.

7.1. Ethical and cultural considerations

Children over the age of 12 who are of sufficient maturity and have the mental capacity to understand the benefits, risks, social and other implications are able to consent to medical treatment (Children’s Act of South Africa No. 38 of 2005). No parent, guardian or care-giver of a child may withhold consent by reason only of religious or other beliefs, unless that parent or guardian can show that there is a medically acceptable alternative. Consent for vaccination may lie ultimately with the young woman/girl but adequate parental information and assent will strengthen a comprehensive cancer prevention programme. Demonstration projects are in progress in South Africa to study a combined screening and vaccination policy for mothers and daughters.

In the US some religious and cultural groups expressed concern about the availability of a vaccine against a sexually transmitted
infection as it could undermine abstinence-based prevention messages. Others counter that while committed fidelity is the most effective way to combat cervical cancer, many people either do not want to make such changes in their personal behaviour or, even if they want to, find it impossible to do so in their personal circumstances. Some express concern for potential harm caused by HPV vaccination, including adverse reactions, a hypothetical reduction in safer sex practices, reduced preventive cervical screening, and a misconception that HPV vaccine would protect against other STIs. All of these factors need to be taken into account before population wide introduction of HPV vaccines in South Africa. Thorough and culturally specific education programmes for providers and the general population is of importance to prevent negative perceptions [66]. The situation in India is one example of a failure in communication that led to the cancellation of a promising programme [67]. The results of a survey done in North Carolina showed that only few parents believed that HPV vaccine would increase sexual activity. Reassuringly, most parents did not believe that a reduction of screening is safe in vaccinated women [68].

8. Introduction of a population based vaccination programme

Internationally HPV vaccines are not marketed as low cost items. In a health economics equation the cost of immunisation must be weighed against the cost of screening and treatment for cervical cancer with the understanding that the cost saving benefits of immunisation will only become apparent in one to two decades. The principle of justice dictates that medical care should be available to all who need it including economically disadvantaged communities.

A recent calculation of cost effectiveness of introducing HPV vaccination performed in South Africa found that the price of the vaccine (taken at $120 a dose for the purpose of the calculation) was the main cost driver. A price reduction of 60% or more would make vaccine-plus-screening more cost effective than the screening-only option [69]. The current cost of a single dose of the bivalent vaccine in private retail pharmacies is around $70 and around $110 for the quadrivalent vaccine. Cooperative buying and bargaining may reduce vaccine cost and one example is the Pan American Health Organization (PAHO) Revolving Fund. Members of PAHO can buy the HPV vaccine at a reduced cost per dose of around $17 [65].

8.1. HIV infected

Studies on HPV immunisation in HIV infected individuals are not readily available. The efficacy of HPV vaccination in immunocompromised individuals is largely unknown. It has been suggested that natural immunity against HPV will be lost as immunity deteriorates and this may also be true for immunity acquired by vaccination. HIV infected women are at more risk of rapid progression to cervical cancer when they acquire oncogenic HPV infections. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention states that the quadrivalent and bivalent vaccines “are not live vaccines, and can be administered to females who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons” [70]. HIV testing prior to immunisation should be discouraged because it may jeopardise uptake.

9. Programmatic issues for South Africa

Vaccination of older children/young adolescents is not common in developing countries. Pilot studies are necessary in advance of a national immunisation programme. The studies should serve as evidence for the South African government on how to introduce HPV vaccination into the preventive armaments of health programmes.

Schools serve as trusted sources for education and could be used for conveying carefully crafted health messages about HPV and vaccination. School based immunisation programmes are the most promising vehicle for a HPV vaccination programme. HPV vaccination could be offered in primary schools to girls attending grade 5 or 6. South Africa has a National School Health policy administered within the Department of Health. Sexuality and reproductive health are already incorporated into the life orientation curriculum in schools. The less than ideal service for youth health has been identified as one of the key deliverables by the Minister of Health in a recent budget speech.

The Expanded Programme on Immunisation (EPI) is well established in South Africa and could serve as a possible home for HPV vaccination. At age 12 the HPV vaccine could be administered with diphtheria/tetanus booster (dT) which is already in the EPI programme. The cold chain remains a highly vulnerable and critical part of a vaccination programme. The Department of Health has developed a cold chain and immunisation operations manual based on the WHO tool for assessing vaccine handling and management.

10. Conclusions

During the past 20 years tremendous insight into the oncogenic process leading to invasive cervical carcinoma has been gained. Major progress has also been made in the understanding of the oncogenic potential of the HPV virus. At the end of 2002 the first HPV16 VLP vaccine trial was published where prevention of infection was proved [71]. In a population where childhood immunisation is already a way of life, even in rural South Africa, HPV vaccination may be the best solution for a very serious problem. It would be unethical not to advocate for HPV immunisation. At the same time screening should continue and programmes for the diagnosis and treatment of premalignant disease should be strengthened.

There is generally good trust in the medical system and vaccination is a part of life in most rural and urban communities. Schools and the education system are also generally regarded as reputable and could be ideal partners in adolescent vaccination. At present there are demonstration projects to evaluate the introduction of a school based adolescent vaccination programme. There are discussions between professional advisory groups and the government about a national cervical cancer prevention strategy that will include vaccination. Despite competing health priorities, of which the management of the HIV epidemic and the control of tuberculosis are two of the most pressing, cervical cancer prevention is seen as a high priority.

South Africa is often regarded as economically similar to the BRIC countries (Brazil, Russia, India and China). Brazil registered both HPV vaccines in 2009. In a joint publication by the International AIDS Vaccine Initiative and the Programme for Appropriate Technology in Health (PATH) it was calculated that HPV vaccination at a cost of $10 per girl will contribute 0.03% of public spending on health [72]. There is no government funded programme in Brazil at time of writing. In India, a large post-licensure observational study was suspended by the government as a precaution after concerns about safety was raised [67]. There are no indications of a national vaccination policy in the near future. In the Russian Federation both vaccines are registered but there is no national programme [73]. In China the prophylactic HPV vaccines are not licensed yet but phase III trials are in progress. A per-dose HPV vaccine cost...
of approximately less than $9–14 would be required for strategies involving vaccination to be cost-effective [74]. If South Africa can move forward rapidly with policy and financing for prophylactic HPV vaccination it may become *Primus inter pares*.

It is clear that for a well-functioning cervical cancer control programme, a good interaction between different disciplines and services is required, including sexual and reproductive health, adolescent health, immunisation, and cancer control [75]. HPV vaccination could be regarded as the nucleus for developing and strengthening the adolescent immunisation programme and overall adolescent health services. With a good functioning immunisation programme and school system being present in South Africa, the major ingredients should be available to develop a comprehensive programme to combat cervical cancer.

**Conflict of interest statement**

None declared.

**References**


Review

Introduction of inactivated polio vaccine (IPV) into the routine immunization schedule of South Africa

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A B S T R A C T

South Africa is currently the only country on the African continent using inactivated polio vaccine (IPV) for routine immunization in a sequential schedule in combination with oral polio vaccine (OPV). IPV is a component of an injectable pentavalent vaccine introduced nationwide in April 2009 and administered according to EPI schedule at 6, 10 and 14 weeks with a booster dose at 18 months. OPV is administered at birth and together with the first IPV dose at 6 weeks, which stimulates gut immune system producing a memory IgA response (OPV), followed by IPV to minimize the risk of vaccine associated paralytic polio (VAPP). OPV is also given to all children under 5 years of age as part of regular mass immunizations campaigns. The decision to incorporate IPV into the routine schedule was not based on cost-effectiveness, which it is not. Other factors were taken into account: Firstly, the sequence benefits from the initial mucosal contact with live(vaccine) virus which promotes the IgA response from subsequent IPV, as well as herd immunity from OPV, together with the safety of IPV. Secondly, given the widespread and increasing use of IPV in the developed world, public acceptance of vaccination in general is enhanced in South Africa which is classified as an upper middle income developing country. Thirdly, to address equity concerns because of the growing use of IPV in the private sector. Fourthly, the advent of combination vaccines facilitated the incorporation of IPV into the EPI schedule.

In April 2009, South Africa introduced three new vaccines into its universal immunization schedule, pneumococcal conjugate vaccine, rotavirus vaccine and a pentavalent vaccine consisting of diphtheria, acellular pertussis, tetanus, Haemophilus influenzae type b and inactivated polio vaccine (IPV). The schedule for the pentavalent vaccine follows the WHO EPI recommended intervals of 6, 10 and 14 weeks, with an additional booster dose at 18 months of age. Presently South Africa is the only country on the African continent which has introduced IPV into its routine EPI schedule.

The last laboratory documented case of wild-type poliomyelitis in South Africa was detected in 1989 [1] and this followed a major outbreak of type 1 poliomyelitis in the eastern province of KwaZulu-Natal the previous year [2]. More recently, however, cases of polio have occurred in countries bordering South Africa and an imported case of polio type 1 was diagnosed in Botswana in 1994 [3] and an outbreak of polio type 1 occurred in Namibia in 1996 [4]. Over the past 3 years some 20 countries on the continent have seen outbreaks of polio imported from Nigeria or India [5] and 4 African countries, Angola, Chad, Democratic Republic of the Congo and Sudan have re-established polio (i.e. circulation of the virus has persisted beyond 12 months) [6]. The risk of importation of polio into South Africa, given the extensive population movement from countries throughout the continent into South Africa as refugees or as work seekers is at least moderate if not high. WHO policy recommendations published in its 2010 position paper on polio vaccines, expressed a firm view discouraging an all-OPV strategy [7]. Similarly a WHO African regional meeting in 2008 recommended not to introduce IPV in the region [8]. The decision to introduce IPV into the routine schedule of South Africa was thus taken against this backdrop and this paper examines the factors taken into consideration when the policy switch was made in 2008.

1. Increasing global use of IPV

Although universal immunization with oral polio vaccine (OPV) has been responsible for the elimination of polio in a major portion of the world, an increasing number of polio-free developed countries have now replaced OPV with IPV in their routine immunization schedules, primarily because of the risk of vaccine-associated paralytic polio (VAPP). Thus in 3 WHO regions, which have been certified as polio-free, 69 of the 124 (56%) countries use IPV alone for routine immunization [9]. Of the remaining 3 WHO regions, 9 countries

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by both IPV and OPV [16] and effective intestinal immunity was ineffective in a community which was reliant on IPV alone, the immunization programme which was carried out at intervals of 6, 10 and 14 weeks which is generally used in the developed world [11, 12]. This was probably due to the influence of passively acquired maternal antibody and perhaps also to the shorter interval between doses in the EPI schedule.

2. IPV and OPV combinations

The first country to introduce the combination of IPV and OPV was Denmark in 1968 [13]. The rationale behind the combined schedules is to benefit from the excellent gut mucosal immunity and therefore effective herd immunity provided by OPV while, at the same time, minimizing the risk of VAPP and ensuring good humoral immunity, and thus personal protection, through the use of IPV. Different combinations of IPV and OPV have been evaluated in clinical trials and have been implemented in different countries. Essentially there have been 3 approaches. Firstly, sequential schedules where IPV is given first to protect against the risk of VAPP followed by OPV to provide good gut mucosal and herd immunity. The superiority of this schedule for type 1 and 3 responses has been evaluated in a number of developing countries such as Gambia, Oman and Thailand [12] and it is now used in most countries which employ a combined schedule. A second combination schedule reverses this sequence. Here OPV is given first and is then followed by IPV. This combination schedule has been adapted in South Africa where two doses of OPV are given at birth followed by a second dose at 6 weeks together with the first of the IPV doses in the pentavalent vaccine. Subsequent doses of pentavalent including IPV are then administered at 10 and 14 weeks with a booster at 18 months. Further OPV supplementation takes place through mass immunization programmes which are carried out at intervals of approximately every 3 years and involve all children under 5-year of age. The scientific rationale for administering OPV as the initial dose is based on the finding that IPV immunization is significantly more effective if preceded by contact of the gut mucosal immune system with a live virus infection (such as OPV) and production of IgA [14]. The relatively poor ability of IPV alone to effect a significant gut immune response is greatly enhanced by preceding gut contact with live polio vaccine resulting in the production of a strong memory IgA response. The risk of VAPP from the administration of OPV at birth is extremely low due to the protective effect of maternal antibodies and paralysis due to wild-type polio or vaccine-derived polio has not been reported in infants less than 3 months of age. In addition a neonatal dose is less likely to be affected by interference from endogenous intestinal viral flora. A similar schedule has been practised in the West Bank and Gaza (Palestinian authority) since 1978 [15]. In 1988 following an outbreak on polio in Hadera, Israel, in a community which was reliant on IPV alone, the immunization policy was changed to a sequential schedule of IPV followed by both IPV and OPV [16] and effective intestinal immunity was demonstrated [17]. Since 1988 this combination schedule has succeeded in eliminating polio in the West Bank, Gaza and Israel.

A third combination is the simultaneous administration of OPV and IPV, and this has been evaluated in Pakistan where it was similarly demonstrated that simultaneous administration of IPV, together with OPV in the EPI schedule produced a significantly better immune response compared to OPV alone in the routine EPI schedule [12, 18].

3. Cost-effectiveness of IPV

One of the major barriers to the introduction of IPV into the immunization schedule of developing countries has been cost – IPV being several-fold more expensive per dose than OPV, although countries which have switched to IPV regimens have not been influenced by vaccine cost implications. Cost effectiveness studies have only been published from 3 countries, USA, Australia and South Africa [19]. Replacement of OPV with IPV has been calculated to carry an additional cost of between US$740,000 and US$7.2 million per VAPP case averted. The cost-effectiveness calculated as per discounted DALY averted varied between US$61,000 and US$594,000. In all 3 countries it was clear that a switch from OPV to IPV was not cost-effective. The risk of VAPP in South Africa is unclear. While one would expect between 1 and 2 VAPP cases per year (from a birth cohort of 1.08million [20]) only one proven case of VAPP has been confirmed in South Africa [19], despite satisfactory AFP surveillance which was instituted in 1995 [21]. This may well be due to inadequate follow-up or IPV may genuinely be less common in developing countries as has been reported from India [22].

4. Post-eradication endgame planning

A world free of polio can only be achieved with the cessation of the use of OPV because of the risk of VAPP, circulating vaccine-derived poliovirus, cVDPV and, immunodeficient vaccine-derived poliovirus, iVDPV. Because of cost it is probable that most developing countries will simply cease vaccination once the world has been declared to be polio-free. However, because of the potential risks of re-introduction of polio, as small as they may be, either from accidental or deliberate release, many developed countries will not cease immunization in the post-eradication era.

5. Conclusion

South Africa has been classified by the World Bank as an upper middle income developing country [23] and is one of the wealthiest and most developed countries on the continent. Nevertheless South Africa resisted introducing IPV into its routine immunization schedule for several years because of the risk of importation from other African countries, especially given the extent of population migrations. The resistance to change from an all-OPV vaccination policy, supplemented with regular mass immunization campaigns, was due to the need to ensure reliable and sustained intestinal immunity and herd protection. Nevertheless, for a number of cogent reasons the country’s Department of Health was advised to introduce IPV in a sequential schedule into the routine vaccination programme. It was first introduced as a component of a pentavalent vaccine in September 2008 to a limited extent in the Eastern Cape Province and countrywide in April 2009.

These reasons include the following:

(i) Firstly, a neonatal dose of OPV (when the risk of VAPP is very low, if not unknown) and a second OPV dose at 6 weeks would stimulate the gut immune system to generate a solid intestinal IgA response and immunological memory when IPV
is subsequently given at the EPI intervals. In addition, mass immunization with OPV provides supplementary immunological contact with OPV.

(ii) Secondly, introduction of IPV contributes significantly to building public confidence in the vaccination programmes given the widespread use of IPV in the developed world.

(iii) The increasing use of IPV in the private sector created an equity discord with the public sector which could have further damaged confidence in the vaccination programme.

(iv) The advent of combination vaccines incorporating IPV simplified multi-antigen administration and also facilitates the introduction of other needed new vaccines, such as acellular pertussis.

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References


Review

Combination vaccines in the South African setting

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A B S T R A C T

The number of vaccines available and included as part of the national immunization schedules, has increased significantly over the past few decades. This impacts on patient/parent compliance and creates a challenge for health care providers for implementation of schedules necessitating training and infrastructure improvements. Use of combination rather than component vaccines offers advantages for compliance by single dose administration of various antigens, reducing stock costing as well as reducing cost of additional health care visits. Combination vaccines are often significantly more expensive than individual constituent vaccines. Concerns regarding an increased incidence of adverse events with use of combination vaccines have not been confirmed and rates may seem high as the adverse events seem to mimic the sum total of adverse event rates for each individual antigen used but may in fact be lower. Manufacturers typically advise against interchange use of vaccine products. Despite this, health authorities advocate use of an alternative vaccine where the original vaccine in not available, to ensure continuity of vaccination. A notable exception is the acellular pertussis vaccine. Partly, because no serological correlates of immunity exist, but also a general lack of convincing follow up studies has prompted the recommendation for manufacturer fidelity for at least the first 3 vaccine doses. According to the South African Medicines Formulary, a variety of vaccines are available in South Africa. Although a large number are available in the private sector, the only true combination vaccine included in the current state EPI, modified in 2009, is the DTaP-IPV/Hib vaccine (Diphtheria, Tetanus, acellular Pertussis, inactivated Poliomyelitis virus and Haemophilus influenzae type b). There are many reasons justifying the use of combination vaccines rather that the individual constituent formulations. Implementation of use in the South African setting at this point is still limited, but may offer an exciting avenue of expanding the antigen repertoire without impacting on side-effects, efficacy or complexity of scheduling.

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1. Introduction

The number of vaccines available and included as part of the national immunization schedule, has drastically increased over the past few decades [1,2]. This not only impacts on patient/parent compliance, but also on the complexity of schedules, making implementation progressively more difficult [3]. Since the first combination vaccines became available in the 1940s in the form of DTP [4], there has been a drive to increasing the amount of antigens captured within single administration doses, with preservation of vaccine efficacy [5]. Initial efforts included reconstitution of various component just prior to administration [6,7], dual-chambered syringes which is mixed just prior to administration [8] to present day true combination vaccines with individual components merged at time of production [9].

Development has been subject to many teething problems. Chemical incompatibility was the first major obstacle noted with use of thimerosal as preservative in whole cell and some acellular pertussis vaccines, detrimentally impacting on the immune response to IPV. Although current Hib vaccines have not been subject to carrier-induced epitope suppression, this was a significant problem in previous formulations. The issue of carrier-induced epitope suppression is specifically noted in certain bacterial pathogens with multiple serotypes causing disease. This requires inclusion of a multitude of conjugates into the vaccine, leading to a diminished immune response, particularly upon booster doses [10]. Furthermore, antigenic competition in formulations containing more than one related live virus (notably OPV and MMR) required adjustment of titres to ensure adequate response to all strains [11].

Use of combination vaccines is advocated by the American Advisory Committee on Immunization Practices (ACIP) rather than component vaccines as they offer the possibility of reducing issues surrounding compliance by single dose administration of various antigens [5]. Furthermore, it has the potential advantage of reducing...
2. Implementation considerations

2.1. Compliance and vaccination timeliness

There is no doubt that the availability of vaccines has significantly reduced morbidity and mortality within most communities [1,2]. This has been shown to be a shared sentiment amongst most parents; however, concern is often raised regarding adverse events associated with the high vaccine load administered in one injection [16]. It has been suggested that the conversion from one vaccine to multiple vaccines will improve patient and parent compliance significantly [3,17]. Meyerhoff and Jacobs showed that up to 26% of patients deferred one vaccine dose when 3 or less injections were indicated, with the deferral rate increasing to 48% when the doses increased to 5 injections [18].

The most frequently cited reasons for vaccination deferral include the number of injections, complexity of the dosing schedule and pain or discomfort experienced [19]. Therefore, use of combination vaccines has shown to improve on timeliness of vaccination (decreasing deferrals), and therefore coverage rates per age [20,21].

From the health care provider's perspective, combination vaccines are also well received, citing increased staff efficiency, ease of record keeping and improved relations with parents and patients, and therefore compliance as significant advantages to this practice [3]. From a health and safety perspective, handling of fewer sharps also reduces the risk of occupational exposures by staff and personnel [22].

2.2. Financial implications

Vaccines are considered the most cost effective tool for prevention of infectious disease [23]. Therefore, the true issue surrounding vaccination is not whether or not to implement immunization, but rather acquisition of the most cost-effective formulations. Combination vaccines are often more expensive than individual constituent vaccines [20]. In fact, pricing has evoked multiple studies leading to pricing algorithms to ensure preferential implementation in vaccination schedules [24]. At present, vaccines other than the 6 original Expanded Programme on Immunization (EPI) formulations as stipulated by the World Health Organization (WHO), are distributed at much higher prices as compared to the EPI vaccines [25]. In light of all these controversies, bulk procurement by Governments, with or without external financial aid by organizations like Global Alliance for Vaccines and Immunization (GAVI), may negate the issues surrounding cost of these vaccines [1]. South Africa is not included amongst the 75 countries receiving support from GAVI [1,26] as the annual per capita gross national income is more than $1000 [27].

Some US based studies place some emphasis on the impact of fewer injections translating in lower administrative costs. This leads to lower charges to the patient but consequently lower income to the clinician [20]. South Africa shows some similarity in that a clear delineation exists between public and private health care, with full vaccination cost being R1 275 [28] and R4 396 (whole sale) respectively. The financial impact of combination vaccines in the South African setting has not been studied.

Despite the enormous success that has been attained by global use of vaccines [29–31], more than 80 million cases of vaccine preventable disease and 1.5 million deaths are reported annually, worldwide [31]. This is by and large due to inadequate delivery and lack of infrastructure and communication within the developing world [31]. Despite this, marked improvement in vaccine coverage has already been attained – in 1974 less than 5% of children worldwide had access to the 6 major vaccines targeting poliomyelitis, tuberculosis, pertussis, measles, tetanus and whooping cough [32]. Since initiation of the World Health Organization's (WHO) Expanded Programme on Immunization (EPI) in 1974 [33], DTP3 rates have increased to 81% by 2006 [24], preventing an estimated 3 million deaths annually [2]. Combination vaccines offer an additional avenue to facilitate global distribution of multiple antigens simultaneously [30], also improving administration safety and relative reduction in biohazardous waste [34].

2.3. Safety and adverse events

Concerns regarding an increased incidence of adverse events with use of combination vaccines have to date not been confirmed. These rates may seem higher as the adverse events seem to mimic the sum total of adverse event rates for each individual antigen used [35–37] but may even have lower rates [11]. However, the reduction in amount of vaccine preparations will lead to decrease in cumulative exposure to stabilizers and preservatives contained in vaccines [35,38], a benefit well worth considering.

Questions surrounding immune system overload by exposure to multiple antigens arose both due to the observation of carrier-associated immunosuppression [15] as well as occasional transient delayed-type hypersensitivity reactions to certain antigens in the MMR vaccine [39,40]. This requires inclusion of a multitude of conjugates into the vaccine, leading to a diminished immune response, particularly upon booster doses [10]. Despite these findings, the effects caused by combination vaccines seem to have a shorter duration of immune modification as compared to individual vaccines administered separately, and should be considered a major advantage [41]. It should also be considered that immunization leads to exposure to a significantly lower number of antigens as compared to infection with the pathogen itself. Hib vaccine typically contains 2 antigens, as opposed to the more than 50 antigens associated with invasive disease [11]. The same can be said for Hepatitis B vaccine containing 1 antigen as opposed to the 4 or more antigens associated with this viral infection [11,42]. Considering that the immune system has been estimated to be capable of responding to >10 million antigens [11,43], immune overstimulation is highly unlikely through the practice of vaccination [11].

2.4. Efficacy

Evaluation of the efficacy of combination vaccines is typically conducted as a non-inferiority-based study format, thereby proving similar efficacy to individual component vaccines [44,45]. These studies need to be interpreted with clear consideration of what the final endpoint of evaluation is [46] as it can reflect in vivo models of antibody geometric mean concentrations [46,47], or epidemiological disease rates [41,48]. Epidemiological proof of effectiveness is defined by the US Code of Federal Regulations as proof through...
controlled investigations, of clinically significant prevention of disease in a significant proportion of the target population [49]. Licensing of combination products are required when either unlicensed components are added to existing vaccines or when licensed vaccines are combined [50]. Licensing procedures aim at ensuring that the act of combining antigens does not negatively impact on purity, potency, safety or efficacy of individual components [51]. Once efficacy has been established to be non-inferior to individual components through preclinical phase 1,2 and 3 trials by manufacturers and licensing has been procured, vaccines use can be implemented [52]. This is followed by extensive post-licensing surveillance during which time the epidemiological impact can be thoroughly investigated [46].

Combination vaccine formulations currently available not only have extensive research backing from manufacturers and independent researchers, but also through independent evaluation of combination vaccines compared to individual components [53–56] as well as effect of administration with additional vaccines at varying time intervals [57,58]. Through this rigorous process, vaccine efficacy is therefore by and large proven, and thereby immunogenicity established.

2.5. Interchangeability of vaccine products

Manufacturers typically advise against interchanging use of vaccine products. Despite this, the ACIP still recommends administration of vaccines from various manufacturers if original vaccine is not available, to ensure continuity of vaccination [5]. A notable exception is the acellular pertussis vaccine. Partly, because no serological correlates of immunity exist, but also a general lack of convincing follow up studies [5,59] has prompted the recommendation for manufacturer fidelity for at least the first 3 vaccine doses [5]. Interchangeability studies are not typically conducted formally, but rather derived from either known correlates for protection or post-licensing surveillance data [60,61].

2.6. Antigen redundancy

Inclusion of combination vaccines into a vaccination programme may lead to over-administration of certain antigens, as these vaccines are less adaptable. Additionally, administration of extra doses of many live-virus vaccines, Hib and Hepatitis B vaccine has not been associated with harmful events [5]. However, certain vaccines, most notably tetanus toxoid [62–68] and pneumococcal polysaccharide vaccine, may cause adverse events if additional doses are administered [69,70] and this practise is therefore not advocated.

3. Local availability and use of combination vaccines in the South African EPI

The South African Medicines Formulary (SAMF) lists a variety of combination vaccines that are available in South Africa (Table 1). Although these are all available in the private sector, the only true combination vaccine included in the current EPI as modified in 2009, is the DTap-IPV/Hib vaccine (Pentaxim™) by Sanofi Pasteur (Diphtheria, Tetanus, acellular Pertussis, inactivated Poliomyelitis virus and Haemophilus influenzae type b) [71,72]. Safety and immunogenicity data has been produced in abundance, including within South African cohorts [73,74]. These studies seem to suggest a favourable safety profile with acceptable rates of adverse reactions [73]. As to be expected, booster doses seemed to show a slightly higher incidence of adverse reactions as compared to primary vaccinations. Local efficacy data is also promising. Recent work by Madhi et al. showed significant protection extending throughout the vaccination period. Following a single vaccine, protective responses could be demonstrated just prior to booster dosing at 18–19 months in more than 97% of patients for tetanus, diphtheria, polio virus and Hepatitis B virus. Although it seemed as though titres for the Haemophilus influenzae type B component PRP had waned, a booster increased titres by more than 400% in more than 95% of cases [74].

South Africa was declared to be free of wild-type poliovirus in 2006 by the Africa Region Certification Commission (ARCC), based on adequate surveillance showing no local cases since 1989 [75]. South Africa is unique in utilizing both IPV and OPV vaccines within the EPI [76]. Since the eventual move to IPV, a more expensive vaccine, has been shown to be cost-effective, the cost of complications of OPV like vaccine-associated paralytic poliomyelitis (VAPP) needs to be considered [77]. Complications like VAPP are very rare, however, certain risk factors may predispose to its development. These include specific immunosuppressive states, most notably congenital agammaglobulinaemia, which has been associated with a single case of VAPP in South Africa in 2011 [78]. Although no other cases have been confirmed in South Africa, numerous cases have been described in other African countries (Nigeria and Ethiopia) [79]. For these reasons, the inevitable change to IPV may be prudent to prevent further cases of VAPP.

A significant reduction in maternal and neonatal tetanus has also been demonstrated and the WHO declared South Africa to be free of disease in these populations in 2002 [75]. Although invasive infection by Haemophilus influenzae type b still occurs, incidence has dramatically declined [80]. Hib vaccine was introduced as part of the South African EPI in 1999 [81]. In a subsequent evaluation looking at the rates of invasive disease caused by Haemophilus influenzae type b from 1999 to 2004, a 65% reduction could be demonstrated [80]. Unfortunately, the impact pre- and post-vaccination cannot be determined reliably as the national laboratory-based surveillance system was introduced in conjunction with Hib vaccination [82]. However, a survey performed in Cape Town in 1994 cited rates of invasive Hib disease amongst <1 year olds, to be as high as 169 cases per 100,000 population [83]. This stand in contrast to 1999–2000 rates of 55 cases per 100,000 population amongst <1 year olds [80]. Efficacy has been shown locally in both outcome-related as well as behaviour-related productivity gains, and use is therefore advocated [84], however contradictory views do exist [85,86].

Use of MMR vaccines is currently not included in the EPI and only measles vaccine is utilized at 9 and 18 months of age [87–89]. The decision to not include rubella vaccine was based on the premise that if sustained high coverage of vaccine cannot be guaranteed, a paradoxical increase the number of susceptible young females could occur. This in turn would lead to an increase in congenital rubella syndrome (CRS) [90,91]. This issue is currently compounded by the lack of formal surveillance for both primary rubella infection and CRS [90]. The MMR vaccine, however, is available in the private sector [80]. Although not formally studied over the greater South Africa, a study conducted in Gauteng revealed private sector vaccination to account for as much as 21% of all cases. Ironically, rates of complete vaccination seem to have been higher amongst attendees of public sector immunization clinics (83%) as compared to private clinics (75%) [92]. It is therefore clear that the private sector should not be neglected in consideration, as it both constitutes a significant portion of the population and current practices are clearly not optimal.

At present, there are some variations offered by the private sector. In terms of combination vaccines, the major difference lies in the availability of Infanrix™ hexa (GlaxoSmithKline) to private patients. In addition to the antigens contained in Pentaxim (Sanofi Pasteur), it also contains Hepatitis B virus surface antigen. The implication is administration of one less injection at both the 6–8 week, 10–12 week and 14–16 week intervals. With regard to other
<table>
<thead>
<tr>
<th>Pharmaceutical name</th>
<th>Target pathogens</th>
<th>Formulation</th>
<th>Constituents</th>
<th>Adjuvant(s)</th>
<th>Primary administration</th>
<th>Special instructions</th>
</tr>
</thead>
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<tr>
<td>Infanrix® DTPa</td>
<td>Diphtheria, Tetanus, Pertussis</td>
<td>Prefilled syringe</td>
<td>Diphtheria toxoid ≥ 30 IU, Tetanus toxoid ≥ 40 IU, Pertussis toxoid (acellular) 25 mcg, FHA 25 mcg, Outer membrane protein 8 mcg</td>
<td>None</td>
<td>3 doses of 0.5 mL, 4 weeks apart, Starting age 6 weeks</td>
<td>Booster at 18 months</td>
</tr>
<tr>
<td>Diftavax®</td>
<td>Diphtheria (reduced dosage), Tetanus</td>
<td>Prefilled syringe</td>
<td>Diphtheria toxoid ≥ 2 IU, Tetanus toxoid ≥ 20 IU</td>
<td>Aluminium hydroxide</td>
<td>3 doses of 0.5 mL, 4 weeks apart, After 12 years of age</td>
<td>Can be utilized as booster from age 6, Repeated boosting every 5–10 years, Only available in public sector</td>
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<td>TdPolio</td>
<td>Diphtheria, Tetanus, Polio</td>
<td>Prefilled syringe</td>
<td>Purified diphtheria toxin ≥ 2 IU, Tetanus toxoid ≥ 20 IU, Inactivated poliovirus types 1–3 at 40, 8, 32 D-antigen units</td>
<td>Aluminium hydroxide</td>
<td>N/A</td>
<td>0.5 mL booster dose every 10 years</td>
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<tr>
<td>Tritanrix-HB®</td>
<td>Diphtheria, Tetanus, Pertussis, Hepatitis B</td>
<td>Single dose vial</td>
<td>Diphtheria toxoid ≥ 30 IU, Tetanus toxoid ≥ 60 IU, Inactivated pertussis bacteria (whole cell) ≥ 4 IU, Recombinant HBsAg 10 mcg</td>
<td>Aluminium salts</td>
<td>3 doses of 0.5 mL, 4 weeks apart, From age 6 weeks</td>
<td>Babies born as carriers of HBV should also receive Hepatitis B immunoglobulin at a different injection site</td>
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<td>COMBACT-HIB®</td>
<td>Haemophilus influenzae type b, Diphtheria, Tetanus, Pertussis</td>
<td>Freeze-dried preparation for reconstitution</td>
<td>Haemophilus b polysaccharide 10 mcg, Diphtheria toxoid ≥ 30 IU, Tetanus toxoid ≥ 60 IU, Inactivated B pertussis ≥ 4 IU, Haemophilus b polysaccharide 10 mcg, Diphtheria toxoid ≥ 30 IU, Tetanus toxoid ≥ 40 IU, Pertussis toxoid (acellular) 25 mcg, Inactivated poliovirus 1–3 at 40, 8, 32 D-antigen units, Purified capsular polysaccharide of Hib 10 mcg</td>
<td>None</td>
<td>3 doses of 0.5 mL, 4 weeks apart, From age 6 weeks</td>
<td>Booster at age 15–18 months</td>
</tr>
<tr>
<td>PENTAXIM®</td>
<td>Diphtheria, Tetanus, Pertussis (acellular), Haemophilus influenzae type b, Inactivated Polio</td>
<td>Two formulations produced with only suspension available in South Africa</td>
<td>None</td>
<td>3 doses of 0.5 mL, 4 weeks apart, From age 6 weeks</td>
<td>Booster dose at 18 months</td>
<td></td>
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<td>Infanrix hexa®</td>
<td>Diphtheria, Tetanus, Pertussis (acellular), Haemophilus influenzae type b, Hepatitis B, Inactivated Polio</td>
<td>Prefilled syringe</td>
<td>Diphtheria toxoid ≥ 30 IU, Tetanus toxoid ≥ 40 IU, Pertussis toxoid (acellular) 25 mcg, FHA 25 mcg, Pertactin 8 mcg, Recombinant HBsAg ≥ 10 mcg, Inactivated poliovirus 1–3 at 40, 8, 32 D-antigen units, Purified capsular polysaccharide of Hib 10 mcg</td>
<td>None</td>
<td>3 doses of 0.5 mL, 2, 3 and 4 months OR If HBV vaccine is given at birth: Administered at 6, 10 and 14 weeks</td>
<td>Booster dose at 18 months</td>
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<td>Twinrix®</td>
<td>Hepatitis A and B</td>
<td>Prefilled syringe</td>
<td>Hepatitis A antigen 720 ELISA units, Recombinant HBsAg 20 mcg</td>
<td>None</td>
<td>Adults: 3 doses of 1 mL at 0, 1 and 6 months, Paediatric: (1–15 years) 2 doses of 1 mL at 0 and 6 months</td>
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<td>Morupar®</td>
<td>Measles, Mumps, Rubella</td>
<td>Prefilled syringe</td>
<td>Measles virus (Schwarz strain in chick embryo cell line), Mumps virus (Urabe AM9 strain in chick embryo cell line), Rubella virus (Wistar RA27/3 strain)</td>
<td>None</td>
<td>Single dose of 0.5 mL</td>
<td>Booster at 4-6 year follow up improves protection</td>
</tr>
</tbody>
</table>
4. Effecting change in the South African EPI

The South African National Advisory Group on Immunization (NAGI) was established in 1993 under instruction of the Ministry of Health. Subsequently, the National EPI was established in 1995. Prior to this, immunization programmes varied between various regions and local governing bodies [75]. This group consists of 14 members, of which 9 are regular members, representing the disciplines of paediatrics, neurology, community health, virology, microbiology, infectious diseases, pulmonology, vaccinology and medicines regulation. In addition, 3 ex officio members from the Department of Health EPI programme is included, as well as a WHO and UNICEF representative [95].

NAGI functions in an advisory capacity and has effected inclusion of Hib vaccine in 1999 [80] as well as the introduction of rotavirus and pneumococcal vaccines [96]. These decisions are based on various factors, including (in decreasing order of importance): mortality, disability-adjusted life years or quality-adjusted life years lost, hospitalizations, equity, overall morbidity and epidemiologic potential. Economic issues are also taken into considerations, to not only ensure affordability, but also sustainability. This does not include formal economic evaluations by the group, but rather use of data generated from local research units [95]. In addition, issues like burden of disease and equity also play a major role in decisions the EPI.

The final decision is taken by the Department of Health, and NAGI therefore simply acts as an advisory board. Of note, over 75% of suggestions formulated by NAGI has been implemented in the local EPI [95].

5. Conclusion

South Africa shows great diversity in terms of socio-economic development and infrastructure. These factors have been shown to directly impact on timeliness of vaccination, where poorer communities classically show lower coverage rates with reduced timeliness [97]. This being said, combination vaccines have been proposed as a cost-effective alternative that owing to its relative ease of administration, should theoretically improve on both timeliness and therefore coverage rates [98]. Despite this, implementation of use in the South African setting at this point is still limited, but it may offer an exciting avenue of expanding the antigen repertoire without impacting on side effects, efficacy or complexity of scheduling.

Conflict of interest statement

None declared.

References


[28] Phosphoko S. Vaccine costing in SA, personal communication.


Hepatitis B (HB) virus (HBV) infection is highly endemic with at least 65 million chronic HB surface antigen (HBsAg) carriers in Africa, 25% of whom are expected to die from liver disease. Before the introduction of the HB vaccine, the prevalence of chronic carriage of HBV in black South Africans was 9.6%, with 76% having been previously exposed to HBV. The major transmission route in South Africa is unexplained horizontal transmission between toddlers, with most transmission occurring before the age of 5 years. During adolescence and early adulthood, sexual transmission becomes the dominant route, while healthcare workers (HCWs) are also at risk for parenteral/percutaneous transmission during occupational exposures. In 1995 the South African Department of Health (SADoH) incorporated the HB vaccine, administered as a monovalent, into the Expanded Programme on Immunisation (EPI) at 6, 10, and 14 weeks of age, and studies conducted thereafter have found it to be safe and highly effective. Catch-up vaccination for adolescents was not introduced and there is no schools-based vaccination programme. The SADoH recommends HB vaccination of HCWs, but this is not mandatory and there is no national policy, thus HB vaccination uptake in HCWs is sub-optimal. Since 1995, studies on children have found that the prevalence of chronic HBsAg carriage has decreased, as has the incidence of paediatric hepato-cellular carcinoma and HBV-related membranous nephropathy. The SADoH should focus their efforts on attaining a high infant HB vaccine coverage, prepare for introducing a HB birth dose, and consider using a hexavalent vaccine (DTaP-IPV-Hib-HepB). The department may also want to consider including targeted HB vaccination for 12 year-olds, if their Road to Health Cards show they were not vaccinated as infants.

1. Introduction

Hepatitis B (HB) virus (HBV) infection is a major public health problem in sub-Saharan Africa. The virus is highly endemic (≥8% HB surface antigen [HBsAg] prevalence) with at least 65 million chronic HBV carriers in Africa [1], 25% of whom are expected to die from liver disease including cirrhosis and hepatocellular carcinoma (HCC) [2]. Although anti-viral treatment for chronic HB can result in viral clearance, for most patients this is not the case, and these treatments are unavailable to the majority of sub-Saharan Africans. Nevertheless, HBV infection is vaccine-preventable, and in 1992 the World Health Organization (WHO) recommended that the highly efficacious HB vaccine should be incorporated into the national Expanded Programmes on Immunisation (EPI) in all countries by 1997 [3]. The majority of African governments (45 of the 46 WHO African Region [AFRO] member states) had incorporated the HB vaccine into their EPIs by December 2010, and the last one (Equatorial Guinea) will do so in the coming months [4,5].

1.1. The prevalence of HBV in South Africa

Prior to the introduction of HB vaccination in South Africa, it was estimated that the prevalence of HBsAg chronic carriage in black South Africans was 9.6%, with 76% having been previously exposed (positive for one or more HBV serological marker) to HBV [2]. In stark contrast, Caucasians and Indians had a carrier rate of 0.2% and a total exposure rate of 5%, whilst those of mixed descent (European-African) had a carrier rate of 0.4–3%, and a total exposure rate of 18–25%, and South Africans of Chinese descent had...
a carrier rate of 5.3% and a total exposure rate of 50% [6]. Generally, prevalence rates vary between rural and urban populations, with a prevalence of HBV chronic carriers in the rural former Transkei (Eastern Cape) of 15.5%, while those in urban areas are much lower: Durban, 7.4%, and Soweto, 1.3% [6]. Although both sexes are equally exposed to HBV, HBsAg carriage is higher in males, with an average male to female ratio of 2.6:1 [7]. It has been estimated that HBV is responsible for approximately 60% of the country’s acute viral hepatitis cases, while 94.2% of black men with HCC had previous exposure to HBV, with 56.5% of them being HBsAg-positive [7].

1.2. Transmission of HBV in South Africa

Perinatal transmission (via percutaneous and permcucosal exposure to the mother’s blood from 28 weeks of gestation up to 7 days after birth, but occurring mainly at or near the time of birth) [8–10] does occur in South Africa. This however is not the major transmission route in the country nor the region as a whole, because of the relatively low frequency of HBe antigen (HBeAg) positivity in HBsAg-positive pregnant women (0–18.6%) [6]. Because HBeAg acts as a tolerogen [11,12], 70–90% of babies born to HBeAg-positive mothers will become chronic carriers of the virus, in contrast to only 10% of babies born to mothers who are HBeAg-negative [13–17]. It was previously thought that breastfeeding may also play a role, but more recent studies have shown this not to be the case [10].

Horizontal transmission between toddlers (i.e. transmission unrelated to recognised sexual, perinalatal, or parenteral exposure [18]) is the major route in South Africa [2,6,19,20]. Although this mode of transmission is largely unexplained, ritual scarification [2,6,19], weeping sores [19], and saliva [2,21] have been implicated. About 20–30% of those horizontally infected before the age of 5 years progress to chronicity [15,16,22]. HBV exposure during childhood can lead to a large proportion of adolescents being infected by the time they reach the age of sexual maturity [20]. Thereafter, in adolescence and early adulthood, sexual transmission becomes the dominant route of transmission [2,6,19,20,22], with 3–5% of those infected at this age progressing to chronicity [15,16,23].

Parenteral/percutaneous transmission is another important route of transmission. Worldwide, unsafe injections and contaminated blood transfusions are responsible for up to 21 million HBV infections each year [24,25]. Most occur in regions of high endemicity. This risk is greatly reduced in South Africa where blood donations are routinely screened for HBV using individual donor nucleic acid testing [26]. Moreover, South African healthcare workers (HCWs) and their patients are at high risk for acquiring HBV infections in the healthcare setting [20,27–29]. As with sexual transmission, parenteral transmission (mainly as a result of intravenous drug use) is an important mode of HBV infection in regions of low and intermediate endemicity, with infections occurring mainly in adolescents and young adults. Thus the mode of transmission in South Africa differs from the mode seen in areas of low endemicity.

2. The prevention and control of HBV

In May 2010, the 63rd World Health Assembly adopted a resolution prioritising the global prevention and control of viral hepatitis [30], of which HBV is the major causative agent in sub-Saharan Africa. A cheap, highly effective inactivated plasma-derived vaccine against HBV has been available since 1982 [3,31]. In 1986, a more expensive recombinant HB vaccine, made by inserting the HBsAg gene into yeasts or mammalian cell lines via plasmids, was introduced. The recombinant yeasts or cell lines are cultured, and the resulting HBsAg proteins are then purified and incorporated into the vaccine. In natural infections, HBsAg is the protein that elicits host production of both neutralising anti-HBs and HBsAg-specific cytotoxic T lymphocytes. Since their introduction, recombinant HB vaccines have gradually replaced plasma-derived HB vaccines, having an excellent immunogenicity and safety profile with infrequent mild adverse events following immunisation (AEIs) [23,32]. Immunisation strategies for the prevention and control of HBV include routine infant immunisation; prevention of perinatal transmission; catch-up vaccination for older age groups; and vaccination of high risk groups, including HCWs [28,31].

If a good immune response was elicited after the primary vaccination course, booster doses for healthy individuals are unnecessary and uneconomical [33–36]. Even if anti-HBs is lost or is not detectable in the serum for 28–31 months post-vaccination, a good anamnestic response is mounted when a previously successfully vaccinated person is exposed to HBV [35]. Furthermore, immune memory has been shown to persist for at least 20 years after successful primary vaccination [37].

2.1. Universal infant HB vaccination in South Africa

2.1.1. Integration of HB vaccination into the Expanded Programme on Immunisation

Because chronic HBV carriage is mainly established in early childhood in South Africa, infant immunisation against HBV has been prioritised, with the South African National Department of Health (SADoH) having introduced the HB vaccine into the national EPI (EPI-SA) in April 1995 [38,39]. The first HB vaccine to be used in the EPI-SA was the plasma-derived Hepaccine B vaccine (Chell Foods and Chemicals, Seoul, South Korea). Despite the excellent safety record of this vaccine, EPI-SA followed global trends and switched to genetically engineered recombinant HB vaccines. Currently, the HeberBiovac HB vaccine (Centre for Genetic Engineering and Biotechnology, Havana, Cuba), which has been shown to be more immunogenic than Hepaccine B in the South African setting [40], or Engerix-B (GlaxoSmithKline, Belgium), are being used. As in most countries in the region, the HB vaccine is given at 6, 10, and 14 weeks of age [17]. While the EPIs of GAVI-assisted countries in the region administer the HB vaccine as part of the pentavalent vaccine against diphtheria, tetanus, pertussis, HBV, and Haemophilus influenzae type b (DTPw-HepB-Hib), EPI-SA administers it as a monovalent vaccine [41].

2.1.2. Effectiveness of HB vaccination in children

Various post-introduction South African studies have shown the HB vaccine to be both highly immunogenic and effective. Children who were vaccinated as infants with Hepaccine B in 1995 and followed up for two to three years, had an initial seroprotection frequency of 93% (anti-HBs >10 mIU/ml). Of the original 186 children, 93 were tested in 1997, and 69 in 1998, with 75.3% and 76.8% still having protective levels of anti-HBs, respectively. None of the children were positive for HBsAg, HBV DNA, or anti-HBc [42]. Field studies on children who, as infants, were vaccinated with Hepaccine B as part of the routine EPI, have shown similar effectiveness. In an Eastern Cape cohort, none of 1213 fully vaccinated (i.e. having received three doses of HB vaccine) 12–24 month-olds born after 1995, were found to be HBsAg-positive, compared to 7.8% (39/498) of unvaccinated 12–24 month-olds born before 1995, who were HBsAg-positive. Furthermore, only 0.3% (4/1213) of the vaccinated cohort were found to be HBV DNA positive, compared to 6.5% (30/459) of the HBsAg-negative unvaccinated cohort, and 84.6% (834/986) of the vaccinated cohort had protective levels of anti-HBs [43]. A study on fully vaccinated 18 month-olds who had been vaccinated in rural districts of all 9 provinces of South Africa, found protective levels of anti-HBs in 87% (669/769), with only...
HAART has recently been raised to 350 cells/mm³, it is hoped that count for the initiation of highly active antiretroviral treatment infant may be horizontally infected [20]. However, since the CD4+ statistically significant [50]. Thus almost 80% of babies born to compared to 54% in HIV-unexposed neonates, a finding that was 21% of HIV-exposed neonates had protective levels of anti-HBs [49].

The coverage of the 3rd dose of HB vaccine (HB-3) in South Africa rose from 74% in 1997 [17] to 88% in 2000 [47]. The latest official HB-3 coverage figure for 2010 is 97% [47], which shows a vast improvement but may be an over-estimation [47]. According to the WHO, HB-3 coverage dropped to 56% in 2007, and has not risen since. However, these coverage estimates are not based on scientific surveys, and a high quality coverage survey has been recommended [47].

2.2. Prevention of perinatal transmission

Recently, the WHO recommended that the EPI of all countries should include a birth dose of HB vaccine, administered within 24 h of birth to stop perinatal transmission [23]. At the time of this recommendation, studies from countries where perinatal transmission is common, such as those in southeast Asia, had shown that administering a birth dose of HB vaccine is highly effective in preventing HB infection in neonates born to HBsAg-positive mothers [48]. However, in sub-Saharan Africa, including South Africa, horizontal transmission between infants and toddlers, and not perinatal transmission, is the most common transmission route, thus adding a birth dose to the current schedule is not immediately apparent as epidemiologically justifiable.

There is concern though, that the relatively high prevalence of HIV in the region may have changed this premise for two reasons: First, HIV and HBV co-infected individuals are more likely to have active HBV infection, and pregnant women with active HBV infection are more likely to infect their babies perinatally [20]. However, a study on 1420 South African antenatal women found no increase in HBV-positives for either HBsAg (6.2% versus 5.8% in HIV-positives) or HBV DNA (2.4% versus 2.2%), although there was a significant increase in the prevalence of HBV exposure in the HIV-positive group relative to the negative group (39.2% versus 30.1%) [49].

Second, a more compelling reason is that there may be a lack of transfer of maternal anti-HBs from immunosuppressed HIV-infected mothers. A recent South African study found that only 21% of HIV-exposed neonates had protective levels of anti-HBs compared to 54% in HIV-unexposed neonates, a finding that was statistically significant [50]. Thus almost 80% of babies born to HIV-positive mothers have no protection against HBV until the first dose of vaccine is received at 6 weeks of age, during which time the infant may be horizontally infected [20]. However, since the CD4+ count for the initiation of highly active antiretroviral treatment (HAART) has recently been raised to 350 cells/mm³, it is hoped that in the future a substantial proportion of HIV-positive pregnant women will be placed on HAART (as opposed to dual antiretroviral therapy for the prevention of mother-to-child transmission of HIV). This will not only prevent HIV transmission, but also, by reducing immunosuppression in the mothers, maternal anti-HBs levels may be conserved resulting in increased anti-HBs transfer to their babies.

Currently the current HB vaccination schedule is not preventing all infant infections in South Africa, as a few breakthrough infections have been reported, mainly in HIV-exposed/infected babies [44,45]. The most recent South African study found that only 1% (3/303) of babies aged 5–24 months were positive for HBsAg, and although 2 of the 3 HBsAg-positive babies were HIV-positive, this finding was not statistically significant [45]. The HIV status of the mothers in this study was unknown.

It is not unreasonable to argue that a birth dose may prevent a substantial proportion of these infections. But first, one must examine the programmatic challenges and opportunities. Administering a HB vaccine birth dose within the EPI-SA is logistically feasible because the current monovalent HB vaccine is suitable for the birth dose and can be administered together with oral polio vaccine and Bacille Calmette Guérin (BCG), which are already scheduled to be administered at birth. However, the HB vaccine birth dose must be given within 24 h of birth, whereas the time of administration of the birth dose of both oral OPV and BCG is more flexible, and therefore sometimes only given within 7 days or even 14 days after birth. Moreover, BCG coverage figures in the more rural provinces of KwaZulu-Natal and the Eastern Cape are relatively low at 79.1% and 70.6%, respectively [51]. This is probably because most rural babies are born at home, and home births are generally not attended by trained HCWs [52].

Next, one must examine the economic opportunities and challenges. In 2009, the EPI-SA cost of fully vaccinating a child was USD 148 in the public sector and USD 454 in the private sector for the vaccines alone [53]. While South Africa is a middle income country that has, since 1994, had the good fortune to have successive health ministers who have all been fully committed to supporting EPI-SA, there are many competing health priorities. For example, the burden of cervical cancer in South Africa is high, yet the country has not yet introduced the highly effective vaccine against the human papilloma virus (HPV) (the cause of cervical and other anogenital cancers). It must also be established how effective the HB birth dose will be at preventing neonatal infections, bearing in mind that birth dose coverage will be lower (and is unlikely to be administered within 24 h [52]) in the rural areas, where the prevalence of HBsAg in HBsAg-positive black pregnant women is 12% [6]. On the other hand, administering a HB birth dose in urban areas, where birth dose coverage is expected to be higher, may in fact not be very cost-effective considering that the carriage of HBsAg in HBsAg-positive black pregnant women born and living in the urban township of Soweto was previously found to be 0% [6].

Thus in light of programmatic challenges and the many competing health priorities in the country with limited resources, the introduction of a HB birth dose, especially for home births in under-resourced rural communities, may not be viewed as a priority at present [52]. Since there are no South African studies which show a reduction in HBsAg prevalence when the birth dose is used, further studies are needed before any recommendations regarding this can be made.

2.3. Catch-up vaccination programmes for adolescents

In regions highly endemic for HBV, the WHO places the most emphasis on implementing universal infant immunisation with high coverage, rather than on catch-up vaccination programmes for adolescents. Only once high coverage rates of infants and young children are achieved should catch-up vaccination for older children be considered in these regions [23]. This is a pragmatic approach for sub-Saharan Africa, because transmission occurs mostly before the age of 5 years in this region, and school immunisation programmes are largely non-existent. According to the most
recently published EPI schedule, EPI-SA is meant to administer a Td (tetanus and reduced strength diphtheria) vaccine to 12 year-olds (Td-12y) [41], who are nearing completion of primary schooling. However, there is no functional school-based immunisation programme through which this can be administered, and coverage for Td-12y is extremely low (EPI-SA, personal communication). Currently, most children below 16 years of age should theoretically be vaccinated as the HB vaccine was incorporated into EPI-SA in 1995, thus it is also logical to consider HB vaccination during secondary schooling at ≥16 years of age. However, by 2013 most children born prior to 1995 should have completed their secondary education, thus there is a very small window of opportunity and it is probably too late for the SADoH to consider this option. Thus, in line with WHO recommendations, strengthening infant immunisation by increasing EPI coverage in subdistricts with sub-optimal coverage should remain the priority for EPI-SA.

2.4. Vaccination of HCWs

HCWs are at high risk for HB infection, and HBV is acknowledged as being a major cause of occupationally acquired viral hepatitis in HCWs [20,27–29]. Conversely, nosocomial transmission of HBV from infected HCWs to their patients can also occur [25,27]. Data on the prevalence of HBsAg in sub-Saharan HCWs is scant. The few studies that have been conducted have found HBsAg-positivity of: 25.7% in Nigerian surgeons (versus 15% in administrative staff) [54]; 11% in Ugandan medical students [55]; 8.1–8.7% in Ugandan HCWs [56,57], and 3.5% in South African HCWs (unpublished study).

In industrialised countries, which are largely in regions of low HBV endemicity, there are policies aimed at preventing occupational and nosocomial transmission of HBV. For example, the European Union (EU) requires all employers to provide information and vaccination to at-risk HCWs [58–61], and it is official policy in many EU countries to vaccinate all newly enrolled HCWs for HBV [33,60,61]. Organisations such as the Viral Hepatitis Prevention Board endorsed this policy, and extended the recommendation to include vaccination of students in their early years of study in the health professions [62]. Similarly, the United States requires that employers offer free vaccination to at-risk HCWs, as stipulated in the Occupational Safety and Health Administration Blood-borne Pathogen Standard [59,63]. When post-vaccination testing shows a sufficient immune response, no booster doses are needed even after subsequent loss of anti-HBs [34,36]. Revaccination of those who fail to respond to the primary vaccination series is recommended, because it has been shown that 30–69% of non-responders respond to a second series [16,60].

In countries highly endemic for HBV, such as South Africa, the occupational risk of contracting HBV is increased. HIV-positivity is a risk factor for acquiring HBV infection; for reactivating HBV infections that were previously cleared; and also for re-infection with HBV in individuals who were previously immune through clearance of natural infection [20]. HBV is about 100 times more infectious than HIV, yet HCWs are generally more worried about HIV, and seldom test for HBV infection after needle-stick injuries [64]. In South Africa, it has been estimated that 46% of hospital beds are occupied by patients with HIV-related illnesses [65]. Of concern is that 63% (121/192) of acquired immunodeficiency syndrome (AIDS) patients in a Gauteng hospital had serological markers of past or present HBV infection, and 40.6% (78/192) had active HBV infections (HBV DNA positive), and were thus highly infectious [66]. A further concern is that HBsAg-negative HBV infection is highly prevalent in HIV-positive patients [20,66,67]. Thus unprotected HCWs exposed to the blood or body fluids of such patients will not receive HBV post-exposure prophylaxis (PEP) unless the source patient is tested for HBV DNA [20]. Unfortunately HBV DNA testing is not routinely conducted on such cases.

Although the SADoH recommends HB vaccination for HCWs, it has not been made mandatory [20,29,68]. An earlier study from Gauteng, South Africa found that the majority of HCWs at high risk for HBV are not vaccinated, with only 21.2% remembering ever being vaccinated [68]. While current research has shown that the situation has vastly improved, with HB vaccination being widely available and 67.9% of Gauteng HCWs having received at least one dose, only 19.9% had received all 3 doses [29]. Clearly, there is a need for a national policy for the prevention and control of HBV in HCWs to be developed and implemented in South Africa.

3. Impact of universal infant HB vaccination on the burden of disease

3.1. Reduction in HBsAg prevalence in children

Just over 20 years ago, a call was made for more research to be conducted on the horizontal transmission of HBV in sub-Saharan Africa, as it was felt that both the impending HIV epidemic and the introduction of HBV vaccination would change the epidemiology of HBV to such an extent, that this information would be lost forever [69]. As it turns out, this prediction has come true. For example, a large South African study conducted just prior to the introduction of the HB vaccine into the EPI, found that 8.1% of 0–6 month old babies, and 8.9% of 7–12 month old babies, were HBsAg-positive; much higher rates than previously reported from South Africa in these age groups [70]. It was speculated that this increase may have been caused by an increased HIV prevalence in pregnant women, resulting in either (a) increased HBV and HIV co-infection with a subsequent increase in perinatal HBV transmission, or (b) immunosuppression in HIV mono-infected pregnant women resulting in decreased transfer of anti-HBs to their offspring [20]. Fortunately the introduction of the HB vaccine in the EPI-SA in 1995 has reversed this trend, with all South African studies on vaccinated children finding low HBsAg carriage, ranging from 0.0% in children with unknown HIV status, to 2.7% in HIV-positive children [38,42,44,45].

3.2. Reduction in HCC

It is too early to measure the impact of HB vaccination on the prevalence of HCC in South African adults. Although relatively uncommon, HBV-associated HCC can present in children in sub-Saharan Africa. A recent South African national audit of children ≤14 years of age, found a decrease in the proportion of HCC in malignant liver tumours between 1988–2003 and 1988–2006 from 35% (68/194) to 27% (77/274), with this reduction being attributed to 10 years of universal infant immunisation [71,72]. The number of malignant liver tumours had increased by 80 cases, and the incidence of HCC had increased by 9 cases over the 3 year period (2004–2006), thus HCC accounted for only 11.3% of new cases. Also, since 68 HCC cases had previously been recorded during 15 years, 13–14 cases would have been expected in these 3 years instead of 9. However, this is not a large reduction when compared to the dramatic reduction in HBsAg carriage found in younger children, and this needs further investigation.

3.3. Reduction in extra-hepatic manifestations of chronic HBV

HBV-associated nephrotic syndrome (NS), particularly membranous nephropathy (MN) which accounts for 86% of HBV-associated NS cases in KwaZulu-Natal, is one of the major extra-hepatic manifestations of chronic HB seen in South African children [73]. A study conducted in a KwaZulu-Natal referral hospital, which is the
only public sector hospital in the province that provides paediatric nephrology services, found an overall decrease in HBV-associated MN in children ≤14 years old, from 1984 to 2001. The average annual incidence rate ratio (IRR) for the pre-immunisation era (1984–1995) was 0.2/10^5, while that for 2000–2001 was 0.03/10^5. Although this decrease was not statistically significant in ≤4 year-olds when comparing the average annual IRR for 1984–1995 (0.16/10^5) to that for 2000–2001 (0/10^5), the probability of finding no cases from 1998 to 2001 was statistically significant (p = 0.01) when compared to finding 23 cases from 1984 to 1997. However, a statistically significant decrease was found in the 5–9 year-old group, with an average annual IRR of 0.46/10^5 for 1984–1995 compared to 0.09/10^5 for 2000–2001. There was also a decrease in the 10–14 year-old group (0.14/10^5 for 1984–1995 compared to 0/10^5 for 2000–2001), but this was not statistically significant [73].

4. Discussion and conclusion

A number of studies have found the HB vaccine delivered through the EPI-SA to be both highly immunogenic and effective, and at current HB-3 coverage rates it is clear that HBsAg carriage in young South African children will continue to be dramatically reduced, if not eliminated. The high prevalence of HIV in pregnant women does not seem to be having a major impact on HBV transmission in neonates and infants as previously feared. However, the finding of 2.7% HBsAg carriage in HIV-positive babies [45] is of concern, even although this is significantly less than levels of above 8% found in a pre-vaccination study on babies of unknown HIV status [70], and needs further investigation. An expedient strategy would be to add HBV serology testing to any current study testing the effectiveness of one of the newest vaccines (either rotavirus or the pneumococcal conjugate vaccine) that have been added to the EPI-SA, in HIV-positives.

While very little criticism can be directed towards HB vaccination within the EPI-SA, some recommendations can be made. Currently infants are receiving 3 injections at weeks 6 and 14: [DTaP [acellular pertussis]-IPV [inactivated poliovirus]-Hib, HepB, and PCV13 [pneumococcal conjugate vaccine, which is only given at 6 and 14 weeks, and then again at 9 months]). In order to reduce the number of injections, the EPI-SA could strongly consider replacing the pentavalent (DTaP-IPV-Hib) with a hexavalent (DTaP-IPV-Hib-HepB), which is available in South Africa [74]. A HB birth dose is recommended when using combination vaccines, presumably because anti-HBs geometric mean titres (GMTs) with a birth dose have been shown to be much higher than without [75]. However, a number of studies have shown good immunogenicity and long-term anti-HBs memory when using a hexavalent (Infanrix Hexa, GlaxoSmithKline, Belgium) without a HB birth dose [75]. A recent South African study has found good seroprotection rates (≥10 mIU/ml of anti-HBs) when administering an investigational hexavalent (Hexaxim, Sanofi Pasteur, France) without a HB birth dose (95.7%) and with a birth dose (99.0%). However, anti-HBs GMTs were considerably lower without the birth dose (330 mIU/ml) than with the birth dose (1913 mIU/ml) [76]. Heberberovic HB, one of the current HB vaccines used by EPI-SA, has a seroprotection rate of 97.8%, and a GMT of 1145 mIU/ml after 3 doses at 6, 10, and 14 weeks [40]. On the other hand, the first HB vaccine used in the EPI-SA (Hepaccine B) had a seroprotection rate of 93.0%, and a GMT of only 258 mIU/ml when administered at the same schedule [77]. The investigational hexavalent performed better than Engerix-B (administered together with DTP-Hib and OPV [oral polio virus] in a third comparative arm of the Madhi et al. study), which elicited a comparable seroprotection rate of 95.4%, but had a much lower GMT of only 148 mIU/ml [76]. When everything is taken into account, if high birth dose coverage of BCG (within 24 h) can be obtained in the rural areas of South Africa, and if it is found that a HB birth dose is cost effective, the best option may be to introduce a HB birth dose, and to use a hexavalent vaccine. Further studies are required before this recommendation becomes policy. In the interim, the EPI-SA should focus their efforts on attaining a high HB vaccine coverage in all districts and sub-districts in the country, and prepare for introducing a HB birth dose, if and when it can be done effectively and efficiently.

Now that 16 years have passed since the introduction of the HB vaccine into the EPI-SA, it is too late to start a programme on mass catch-up HB vaccination for adolescents. However, when a school-based immunisation programme is successfully implemented for Td-12y, given that the WHO estimates HB-3 coverage to be only 56%, the EPI-SA may want to consider including targeted HB vaccination for 12-year-olds, if their Road to Health Cards show they were not fully vaccinated as infants.

In light of the evidence presented here, it is strongly recommended that the SADOH develops a national policy for the prevention and control of HBV in HCWs. This should include testing for HBV status, and HB vaccination during the early years of training, before student HCWs are exposed to patients [60,62]. Pre-vaccination testing will identify those who are protected against HBV (anti-HBs ≥10 mIU/ml) through natural infection (i.e. are also anti-HBc-positive), thus avoiding unnecessary vaccinations. Anti-HBs negative HCWs should be tested for HBsAg, and all chronic HB carriers should be counselled about selecting a career path which precludes them from performing exposure-prone procedures that put patients at risk of HBV transmission [60], and educated about the need to report all HCW-to-patient exposures so that exposed patients can be given PEP for HBV in good time. The remaining unexposed HCWs should be given a full 3 dose course of HB vaccination, and be tested one month after receiving the final dose [33,60]. Non-responders should be re-vaccinated with another 3 doses. Boosters are not necessary if HCWs have an adequate immune response of ≥10 mIU/ml anti-HBs [33–36], although some authors recommend that a booster dose should be given to HCWs with <100 mIU/ml [60]. While mandatory HB vaccination and HBV testing may not be realistic in the South African setting, the national policy should clearly place the onus on the health education institution/employer to ensure that all HCWs are educated about HBV transmission in the healthcare setting, and are offered vaccination, testing, and appropriate counselling or career guidance where necessary.

In conclusion, despite the gaps identified here, the introduction of the HB vaccine into the EPI-SA in 1995 has been a resounding success for the SADOH. Those responsible are to be congratulated for their vision and foresight in making the prevention and control of HBV a priority on the health agenda of the first democratically elected government of South Africa.

Conflict of interest statement

None declared.

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Review

Haemophilus influenzae type b conjugate vaccines – A South African perspective

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A B S T R A C T

Introduction of Hib vaccine is known to positively impact on reduction of both morbidity and mortality in children less than 5 years of age. Incorporation of this vaccine into a National EPI, however, does come at a significant cost, which is especially important in non-GAVI funded countries. Compounded reduction in response in certain patient populations and possible indication of booster doses further impacts on cost-benefit analyses. Despite these issues, South Africa has supplied Hib vaccine as part of the National EPI in the form of a combination vaccine, Pentaxim®, which combines Hib with Diphtheria, Tetanus, acellular Pertussis (DTP) and Poliomyelitis since 2009. Prior to this, another combination vaccine was utilized containing Hib and DTP. This has subsequently lead to a significant reduction in invasive Hib disease post-introduction, therefore largely justifying utilization.

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1. Introduction

Historically, Haemophilus influenzae type b (Hib) was considered the most common severe invasive infection in children younger than 5 years of age [1,2] in industrialized countries [3], causing in excess of 8 million serious infections worldwide [4]. The peak incidence among unvaccinated individuals varies from 6 to 7 months in developing countries [5], to slightly older in developed countries [6]. Hib-related mortality is attributed to meningitis and pneumonia, but invasive disease may also present as epiglottitis, osteomyelitis, septic arthritis, septicaemia, cellulitis and pericarditis [6]. Worldwide studies conducted prior to the introduction of Hib vaccines amongst almost 4000 patients showed that in excess of 90% of patients presented with one of six clinical syndromes. Of these, meningitis accounted for more than half, but other clinical manifestations included bacteremic pneumonia, epiglottitis, septicaemia, cellulitis and osteoarticular disease (with septic arthritis more common than osteomyelitis) [7]. Invasive disease represented only part of the clinical implication, as meningitis is often complicated with hearing impairment, seizure disorders, cognitive and developmental delay, and various other permanent neurological sequelae [8]. Introduction of Hib vaccination has had a major impact on invasive disease in both developing [9–12] and industrialized countries [7,13,14] despite the fact that disease epidemiology differs in these settings (Table 1).

South Africa was the first African country to introduce Hib vaccine as part of the National Expanded Program on Immunization (EPI) in 1999 [15]; the estimated coverage in 2004 was 92% [6]. Comparison of pre- and post-vaccination burden of diseases data is not possible as a national laboratory-based surveillance system for invasive Hib disease was established simultaneously with the introduction of Hib vaccine in 1999 [15]. However, a study from Cape Town in the pre-immunization era performed at an academic hospital reported an incidence rate of invasive Hib disease of 169 and 47 per 100,000 population for children less than 1 and less than 5 years of age, respectively [17]. Based on the national laboratory-based surveillance (which yields only a fraction of the real burden) reported rates of invasive Hib disease in the first year following vaccination were 6.2 and 1.9 per 100,000 population in less than 1 year and less than 5 years old, respectively. Over the period of 2000–2004 rates of invasive Hib disease decreased significantly, by 65% and 71% in less than 1 year old and less than 5 year old [16], indicating the impact of the Hib vaccine introduction in 1999.

Since 2003, the laboratory surveillance system became an active system including enhanced surveillance conducted at sentinel sites in each of the 9 provinces; detection rates of invasive Hib disease remains low, but from 2003 to 2009 the detection rate increased from 0.7 to 1.3 cases per 100,000 population in children less than 5 years old. Most of these cases were in fully vaccinated children (primary series of 3 doses at 6, 10 and 14 weeks of age) [18]. These findings supported the decision to add since November 2010 a booster dose of Hib at 18 months of age as part of the a new pentavalent vaccine [18].

The World Health Organization (WHO) Strategic Advisory Group of Experts recommended worldwide implementation of Hib vaccination, in 2006. They further stated exception from this only if “robust epidemiologic evidence exists of low disease burden, lack of benefit, or overwhelming impediments to
implementation” [19]. Despite convincing evidence collected over more than twenty years, indicating vaccine efficacy [20,21], only 42% of children worldwide had received this vaccine by 2010 [22]. Two main obstacles have been cited for this; firstly the lack of accurate epidemiological data due to various practical issues surrounding disease identification (discussed in text) and secondly, the high vaccine cost [23].

2. Development of Hib conjugate vaccines

Development of the first polysaccharide Hib vaccines started in the 1970s with the only field studies performed in Finland [24]. This was achieved by utilizing the polyribosylribitol phosphate (PRP) subunits of the bacterial capsule [25]. This vaccine showed an 90% efficacy (95% confidence interval of 55–98%) specifically in children older than 18 months [24]. Efficacy in younger children is markedly lower due to the T-cell independent nature of the vaccine response. These formulations were only licensed for use in the United States (US) [26], Canada [27] and parts of Saudi Arabia [28], where more than 10 million doses were administered from 1985 to 1989 in the US alone [13]. By the late 1980s, conjugate vaccines were being developed against Hib disease, and following this, combination formulations were developed containing these Hib conjugate vaccines [29]. These conjugate vaccines were proven to be superior to PRP vaccines as the PRP-only vaccines were poorly immunogenic in children under the age of 18 months [24], lacked a booster response [30] and did not show any reduction in nasal carriage [31]. This was by and large due to the T-cell-independent nature of the immune response to polysaccharides. Based on disease epidemiology where severe infection is typically noted in younger children, an alternative was needed to improve immunogenicity in this target group [6]. The first Hib conjugate vaccine introduced to the market was a diphtheria toxoid conjugate (PRP-D), thereafter altered to the mutant diphtheria toxin conjugate (PRP-HbOC) [7]. Later on, conjugates were developed containing the outer membrane protein of Neisseria meningitides (PRP-OMP) and tetanus toxoid (PRP-T) [32,33] (Table 2). The first vaccines to be commercially produced were formulated as PRP-HbOC, PRP-D or PRP-OMP and effectiveness was established by extensive clinical trials [34]. Subsequently, PRP-T formulations were produced and efficacy and licensing were based on demonstrating equivalent serum antibody levels compared to PRP-OMP and PRP-HbOC. Of note, most formulations currently utilized, conjugate to tetanus toxoid, as the conjugation technology is not protected by patent laws [6]. PRP-D formulations are no longer in clinical use as these vaccines have been shown to have inferior effectiveness, especially in high prevalence disease populations [35].

In December 2007, a voluntary recall of specific Hib conjugate vaccine lots (PRP-OMP Pedvax HIB® and Comband®) by Merck & Co., Inc. (West Point, USA) indirectly lead to generalized reduction in vaccine coverage. The recall was purely precautionary following identification of Bacillus cereus in vaccine manufacturing equipment [36], and subsequent surveillance did not reveal any contaminated vaccine lots [37] or clinical cases of vaccine-associated B. cereus infection to recipients [36]. Subsequent recommendations were to simply omit use of the booster dose, but to continue vaccination otherwise. Despite this, a generalized reduction in vaccine coverage was noted. This finding highlights the importance of clearly communicated guidelines once a change in national policy is necessary [38].

3. Cost, distribution and delivery

Hib vaccine is more expensive than most of the other EPI vaccines. Costs were estimated to be as much as seven times that of measles, polio, Bacillus Calmette–Guérin (BCG), diphtheria, tetanus and pertussis vaccine in 2005 [23] but current prices are 3 to 9 times the cost (S. Phoshoko, Personal communication). By the end of 2004, the WHO reported that only ten countries in Africa included Hib conjugate vaccine as part of their EPI. These countries are Burundi, The Gambia, Ghana, Kenya, Madagascar, Malawi, Rwanda, South Africa, Uganda and Zambia [39]. However, the current state of Hib vaccine use in Africa seems promising as only Equatorial Guinea, Nigeria, Tunisia, Botswana and Somalia are not including Hib in their routine EPI [40]. In January 2000, the Global Alliance for Vaccines and Immunization (GAVI) was launched, with the mission statement, to provide access to vaccines to the 70 poorest countries in the world [41]. Subsequently, this was expanded to the poorest 76 countries [23,42]. The strategy aims to provide these vaccines through collaboration between the WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation, donor governments, international development and finance organizations, the pharmaceutical industry, as well as from the developing countries themselves [41]. By the end of 2010, an additional 91 million children had received a full course of Hib vaccines, they would otherwise not have had access to [43]. One of the requirements for GAVI support is proof of burden of disease [44]. This has been an issue in the past in the Indian subcontinent, where inadequate surveillance data existed to motivate for provision of vaccines [45]. Fortunately, this has fueled research in this field, confirming mortality due to Hib meningitis to be as high as 11% with 30% of survivors suffering subsequent major neurological sequelae [45].

Despite formal inclusion in the respective EPI’s, vaccine coverage varies significantly from as low as 50% (Madagascar) [39] and more recently, Central African Republic (58%), to 99% in Burkina Faso [46]. Evaluation of rates of invasive Hib disease is dependent on National Surveillance systems. Several countries do not make use of this, and those who do, report significantly variable rates. These vary from no reported cases (Congo, Gambia, Guinea-Bissau,
Lesotho, Rwanda, Suriname and Zambia) in excess of 6000 Hib meningitis cases (Burkina-Faso) [46].

4. Mechanism of vaccine protection

Initial efforts to develop a vaccine utilized polysaccharide antigens. This elicits a T-cell independent response, classically characterized by lower antibody titers, low affinity antibodies with the absence of immune memory. Subsequent efforts to conjugate vaccines to proteins, significantly improved the protective response [47]. Clinically, the improved immunogenicity is of particular importance in children under the age of 18 months [24].

It has been established through PRP vaccine studies [48], that antibody levels in excess of 0.15 μg/ml and 1 μg/ml in serum is indicative of short- and long-term protection, respectively [49]. This is due to both the opsonic activity of antibodies [50–52], as well as complement-mediated bacteriциdal activity [51,53]. In addition, the vaccine offered indirect protection by delaying nasopharyngeal carriage and asymptomatic colonization amongst vaccinated infants [54–57]. This provides an additional level of herd immunity [58,59]. For this reason, Hib vaccine is considered to have effectiveness greater than reported efficacy [6]. Various studies have described community settings where unvaccinated children show significant disease reduction, as a byproduct of vaccination of their peers [9,60–63]. Intermittent colonization, however, is associated with development of natural immunity [64,65] and is likely the cause of the natural decline in incidence of invasive disease with age amongst unvaccinated children [66].

HIV-1 positive patients generally do not launch the same degree of immune response to vaccines as their HIV-negative counterparts in terms of antibody titer production [49]. In addition, presence of anti-PRP antibodies may not confer protection within this population group, as in some instances, antibodies have been shown to be functionally impaired [67]. This quantitative and qualitative impairment seems to correlate with degree of HIV-1 disease progression [67,68].

5. Vaccine efficacy and effectiveness

Epidemiologically, Hib vaccine effectiveness is considered as a measure of reduction in invasive disease. Invasive disease is confirmed by culture of H. influenzae type b from blood or cerebrospinal fluid (CSF). However, invasive disease is generally considered as a poor indicator of overall Hib disease. In addition, there is a relatively small fraction of children with other invasive disease forms like Hib pneumonia will be bacteremic. Furthermore, false laboratory negative results may occur due to inherent difficulties in bacterial culture. Hib is a fastidious organism and is highly sensitive to variables pertaining to sampling after initiation of antibiotic therapy, transport delay and incubation conditions [7]. For these reasons using this case definition, the number of clinical cases, may be significantly underestimated [6]. Various authors have suggested alternative diagnostic and epidemiological means, to overcome this problem, including antigen detection methods [69,70] as well as vaccine-probe study designs [71]. Laboratory parameters focusing on both quantitative and qualitative antibody characteristics have been suggested as markers of protection against disease [72–76]. This is in light of the fact that immunoglobulin quantity [77], subtype [73,76] and avidity [72–75] all contribute to the protective effect.

The WHO advocates that all countries should measure the impact of Hib vaccination in their setting, if practically permitted [78]. The aim with this is not only to determine the vaccine performance under field conditions in general, but specifically within certain population groups. Of particular interest is HIV-1 positive individuals, as vaccine efficacy may be reduced [79]. Proof of effectiveness within a specific population aids in justifying use of these vaccines as part of national guidelines, seeing as this vaccine is in general more costly than most other vaccines included in the EPI. To determine effectiveness of Hib vaccine, a high-quality population-based surveillance system is required to be in place, to collect data from both pre-vaccine and post-vaccine periods [78]. The South African National Surveillance system was established the same year as introduction of Hib vaccine into the EPI in 1999 [18]. Therefore, pre-vaccination data is restricted to studies not performed on national level [17]. Of note, all countries that have included Hib vaccines as part of the national vaccination schedule have shown a significant reduction in invasive disease [14, 21, 80]. As part of an extensive meta-analysis performed by O’Loughlin et al. [78], vaccine efficacy against invasive disease was found to be 95% (95% CI 82–99). This corresponds well with a Cochrane review on this matter [81], as well as various geographically diverse studies [9, 82–87].

6. Hib vaccination and HIV-1 populations

At present, there are an estimated 3.4 million HIV-infected children under the age of 15 years, with 390,000 children newly infected per annum [88]. Of these, less than 10% receive the ART they require [89]. Amongst these patients, one in three children will demise before one year of age, from various causes, including serious bacterial infection [90]. HIV-infected children are at a significantly higher risk of developing bacteraemic pneumonia than their HIV-negative counterparts [91]. In the absence of ART, use of co-trimoxazole prophylaxis has been shown to reduce mortality by as much as 43% [92]. It is postulated that is due to prevention of invasive bacterial infection [93]. This practice, however, requires daily administration of antibiotics for prolonged periods of time, and therefore preventative vaccines may have a major impact in reducing mortality in this respect [93]. The WHO recommends use of all routine vaccines in HIV-infected patients with some notable alterations [94]; firstly evaluation of risk for disseminated BCG [95], and secondly earlier administration of measles vaccine owing to reduced maternal antibody levels for placental transfer [96]. Additionally, due to the inherent immunosuppression noted in HIV-infected individuals, effectiveness of vaccines, in general, has been described to be reduced [79], often necessitating booster doses [93].

Very limited data is available on Hib vaccine effectiveness within settings with a high HIV-1 seroprevalence. Attempts to study vaccine performance have been published from Malawi [84] and Kenya [97], showing either very low patient numbers or low HIV-1 seroprevalence, respectively. Most of our currently understanding of Hib vaccine in this population, comes from a study performed in South Africa. In this study, it is evident that vaccine effectiveness is reduced amongst HIV-infected patients, although still showing moderate activity (55% disease reduction versus 91% amongst HIV-1 negative patients). The HIV-1 rate used in this study was obtained from antenatal clinic attendee data, and therefore, vaccine efficacy may have been underestimated [93]. Furthermore, the risk of vaccine failure was estimated to be 35 fold higher (95% CI 14.6–84.6) for HIV-infected patients [67]. The reason for this seems to be due to a reduction in both quantity and quality of Hib antibodies [67]. In the South African study, HIV-infected children not only had a significantly lower geometric mean antibody concentration 1-month post-immunization, but also lower rates of HibPS antibody concentrations to enable a 50% serum bactericidal activity [67]. Notably, booster doses of Hib vaccine have shown a subsequent improvement of antibody titers to protective levels [98,99], and some authors advocate this practice, although optimal timing of vaccination has not been established. However, the use of
antibody level as a marker of protection within this patient population has been questioned by some authors [93] and more extensive studies are therefore warranted [93].

7. Hib vaccines and South Africa

South Africa is not included as one of the GAVI funded nations [43]. Despite this, it was the first African country to self-finance inclusion of Hib conjugate vaccines as part of the EPI since 1999 [16]. Furthermore, the most recent EPI schedule, as implemented in 2009, also includes a booster dose at 18 months [100] as part of the pentavalent vaccine (Pentaxim®) [101].

From introduction to the South African EPI in 1999, Hib vaccine was administered as part of a combination formulation with Diphtheria, Tetanus and whole cell Pertussis (DTP). Although monovalent formulations of the Hib vaccine are available, various combination vaccines offer the advantage of fewer injections without compromising on the number of antigens administered [102]. The Centers for Disease Control and Prevention recommends two (PRP-OMP) to three (PRP-T) primary doses, in monovalent or combination form, with a booster dose at 12–15 months. Licensed vaccines may be used interchangeably, in order to complete the vaccination series. Of note, the Hiberix® formulation (GlaxoSmithKline, Bryanston, South Africa) is only registered for use as a booster, and not for primary vaccination [102]. The EPI currently in effect, as stipulated in April 2009 utilizes the Sanofi Pasteur vaccine, Pentaxim®, which is a combination vaccine for DTP (acellular formulation), Hib and Poliomyelitis. Since first being marketed in 1997, more than 100 million doses have been administered in over 100 countries, of which 23 have included it as part of the local EPI [103]. GAVI-supported countries use the pentavalent formulation, which contains Diphtheria, Tetanus, whole-cell Pertussis, H. influenzae type b and Hepatitis B virus. This formulation is less expensive but does have a worse side-effect profile owing to use of whole-cell as opposed to acellular Pertussis [42].

There has been a significant reduction in cases of invasive Hib disease since the introduction of the Hib vaccine. This trend is most obvious within the below one year of age population group. Risk factors for developing invasive Hib disease were identified as HIV-1 infection and incomplete vaccination. Despite the clear correlation between Hib-infection and risk of vaccine failure [67], vaccine failures have not been described in other high HIV-1 seropositivity settings [104]. The changes made within the national vaccination recommendations, are also supported by an improved surveillance system. This laboratory-based surveillance system identified that the incidence of non-typable H. influenzae was higher amongst HIV-1 infected patients, and laboratory tested antimicrobial resistance was becoming increasingly important [16]. It did not allude to the bimodal vaccine failure pattern described previously in South Africa amongst HIV-infected patients [91,105]. The introduction of the booster dose was prompted by resurgence of invasive Hib disease, which was ascribed to vaccine failure [18]. It will, however be interesting to observe the impact of the booster dose, as introduced in 2009, on the epidemiology of invasive Hib disease amongst HIV-1 infected and uninfected children.

8. Conclusion

The global acceptance of Hib vaccines has led to major reduction in global disease burden, directly impacting on morbidity and mortality [7]. As the relatively high cost of incorporating this vaccine into any national immunization schedule invariably becomes an important determinant for use, external funding to poorer countries is essential to ensure adequate vaccine coverage to effect the same disease reduction to all.

The high sero-prevalence of HIV-1 in South Africa compounds issues surrounding Hib disease prevention, as HIV-infected children seem to show a more rapid waning immunity as compared to their HIV negative counterparts. This, combined with a higher risk of invasive Hib disease in HIV-infected individuals, is cause for concern. The impact of the booster dose of Hib vaccine administered at 18 months remains to be seen as the hope is that this will provide benefit not only to partially vaccinated patients, but also unvaccinated individuals by providing an additional vaccination opportunity in the second year of life [18].

Conflict of interest statement

None declared.

References


C57


When, and how, should we introduce a combination measles–mumps–rubella (MMR) vaccine into the national childhood expanded immunization programme in South Africa?

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A B S T R A C T
This article briefly reviews the history and epidemiology of measles, mumps and rubella disease and the case for introducing combination measles–mumps–rubella (MMR) vaccine into the national childhood immunization schedule in South Africa. Despite adopting the World Health Organization's Measles Elimination strategy in 1996 and achieving a significant decrease the incidence of measles, added effort is needed in South and southern Africa to reach the goal to eliminate endogenous spread measles. Mumps is still a common disease of childhood and while there are few sequelae, even the rare complications are important in large populations. Congenital rubella syndrome is seldom reported, but it is estimated that of the millions or so children born every year in South Africa over 600 infants are affected to some degree by rubella infection. The naturally acquired immunity to rubella in women of childbearing age in South Africa has been estimated at over 90%, so that introducing a rubella containing vaccine in childhood may paradoxically increase the proportion of girls reaching puberty still susceptible to rubella. The elimination of endogenous measles and rubella is being achieved in many countries in South America, and despite the recent measles epidemic, must still be seriously considered for South and southern Africa. Current constraints and potential steps needed to reach the goal in South Africa are discussed.

1. Introduction

After polio eradication the one of the most sought after goals in child health is the elimination and eradication of measles together with rubella and eventually mumps. The achievements of the World Health Organization, of the Pan American Health Organization and many other country immunization programmes, of UNICEF, of Rotary, of the vaccine manufacturers, of the researchers and of the major donor organizations over the past three to five decades gives good cause to hope, that elimination and eradication of these four diseases within the next three to five decades is indeed more likely than it is not. MMR vaccine is one of the keys to such success.

2. Measles

"Count your children after the measles has passed" is an old Arabic proverb. The disease was described as distinct from small pox by the Persian physician Rhazes in the 10th century as “more dreaded than smallpox” [1]. The devastating nature of measles in previously unexposed populations, also in the Cape Colony in the 18th century, as described by Drutz and Morley, confirms this observation [2,3].

In the pre-vaccination era measles was estimated to cause six million deaths per year mostly in developing countries [4]. More recently WHO estimates of measles deaths globally have dropped from 733 000 in 2000 to 164 000 in 2008 and the aim to eliminate measles in six out of five WHO regions by 2020 does seem feasible [5].

Measles vaccine was officially introduced into the national immunization programme in South Africa in September 1975 and MMR vaccine into the private sector about the same time. From 1981 to 1990 there were between 15 000 and 22 000 clinical cases, and between 250 and 500 deaths, notified annually. In 1990 the Health Department at the time undertook a mass measles campaign and in 1991 the cases dropped to 4777 and the deaths to 29. In 1992, however, the number of measles cases rebounded, in slightly older children, with almost 23 000 cases and 53 deaths [6].

Following a WHO assisted review of the national immunization programme in South Africa in December of 1993 there was a significant strengthening of the whole of this programme which became known as the Expanded Programme of Immunization (EPI SA) [7]. The global polio eradication strategy and the measles elimination strategy were adopted, and a combined polio and measles...
mass immunization campaign was launched in 1996 involving all children 6 months to under 15 years. This was followed by similar campaigns in 2000, 2004 and 2007 in all children 6 months to under 5 years. The incidence of measles dropped dramatically, with almost no cases or deaths being notified in 1997 and from 1998 to 2003 an average 30 cases a year, and no deaths, were reported. Between 2003 and 2005 there were several outbreaks of measles in the provinces of Gauteng, KwaZulu-Natal and the Eastern Cape with a few cases in the Cape Town area. A total of 1676 cases and 27 deaths were reported [8]. In 2006, 2007 and 2008, there were, respectively, 83, 30 and 40 measles cases were confirmed but no deaths reported to the National Institute for Communicable Diseases [9].

After the first mass campaign in 1996 most young health professionals in the country had never seen a case of measles, until about half way through 2009, when a scattering of reported cases around Pretoria and Johannesburg became a full blown epidemic, peaking in Gauteng in mid-October 2009 and in the rest of the country in mid-April 2010. Professor Lucille Blumberg of the National Institute of Infectious diseases in Johannesburg reported that at least one young doctor was admitted to intensive care with complications of measles. This was the first major country-wide measles epidemic in almost 17 years, with a total of over 18 000 laboratory confirmed cases reported by the time the epidemic tailed out in the middle of 2010 [10].

The response to this epidemic was to move forward the planned mass campaign for measles and polio firstly in Gauteng then to the other provinces, and as older age groups were involved, to include the age groups 6 months to 15 years. The case fatality rate from measles in this epidemic reported by the Western Cape Provincial Health Department on March 16th 2010 was about 1% (8/765) [11]. As part of a review of the epidemic and campaign at the National Institute for Communicable Diseases (NICD) in Johannesburg in May 2011 it was recommended more work was needed to expand immunization coverage, to ensure effective information, education and communication and to strengthen surveillance and contact tracing, especially in informal areas around the towns and cities [12].

3. Mumps

Hippocrates described parotitis and orchitis in 500 BC [1]. In the pre-vaccine era, mumps epidemics were reported usually from schools, prisons, ships and military barracks about every 2–5 years. The sero-prevalence of mumps antibodies in pre-vaccine era was between 50 and 90% globally. The introduction of MMR vaccine dropped the incidence of mumps dramatically, though in recent years several epidemics of mumps were reported in university students in the UK and the USA [13,14]. McIntyre and Keen reported on 11 360 cases of viral meningitis investigated in Cape Town between 1981 and 1989 and found that 9% were due to mumps. The average age in this series was 3 years [15]. Complications from mumps such as orchitis (20–50%) and encephalitis (15%) are common but usually with full recovery. Permanent deafness occurs in 1:20 000 cases and is permanent [1]. Mumps is inconvenient and uncomfortable, and costly if admitted to hospital and while the sequelae of mumps maybe rare, in large populations these become significant especially if preventable [13].

4. Rubella

Rubella was first identified as distinct from measles by German physicians in the early 19th century. Rubella like mumps tends to occur in periodic epidemics in pre-adolescent children [1]. Congenital rubella syndrome (CRS) was recognised for the first time in 1940 in Sydney Australia by an ophthalmologist, Norman Gregg, who after overhearing mothers of infants with congenital cataracts share in the waiting room that they had had rubella while pregnant, did a record review and linked an unusual increase of congenital cataracts, and later of congenital heart disease and deafness in infants, to an epidemic of rubella which had spread to the population from a local army camp [16].

The global toll of CRS in 2000 was estimated at 100 000 cases per year [17]. In South Africa, it has been estimated that of the million or so children born in 2005, 654 or 16 to 69/100 000 live births were affected to some degree by congenital rubella infection [18]. Diagnosing congenital rubella is difficult. Those who are picked up early, tend to have a congenital cataract or a serious heart lesion. Sometimes a CRS related defect is only suspected when a child finds school work difficult [19]. So that even if not of widespread public concern, introducing MMR vaccine into the South African immunization programme seems to make sense both from a humanitarian and a cost perspective [20].

Replacing measles vaccine with MMR should not pose significant logistic or health budget problems. Even though the current public tender price for measles vaccine is about US$0.30 a dose in a 10 dose measles vial, and whole sale cost of single dose MMR vaccine to the private sector is currently about US$14.30, the government tender the prices should be closer to UNICEF tender prices—currently between US$1 and US$2 a dose [21]. And despite MR vaccine being half the price of MMR, it seems sensible to use MMR vaccine to avoid both the disease and the rare sequelae. And with more manufacturers starting to make the newer vaccines, the tender prices for rotavirus and pneumococcal vaccines in South Africa are likely to decrease, so that the cost of MMR should not have health budget implications.

Almost 70% (130/193) of other WHO member states have replaced measles vaccine with the combination measles, mumps, rubella (MMR) or measles–rubella (MR) vaccine, the question must be asked, “If there are relatively inexpensive MR or MMR vaccines have been introduced into the childhood immunization programme of majority of countries, why hasn’t South Africa?“ [22]. The problem is that unless routine immunization programmes can demonstrate the ability to consistent achieve a high national immunization coverage for measles vaccine in all sub-districts, introducing rubella vaccine to the childhood immunization schedule is likely sooner or later to lead to an increase of congenital rubella syndrome, as has indeed happened in Greece and Brazil [23,24]. Thus demonstrating in practice that partial immunization coverage with rubella vaccine results in an increase in CRS. Schoub et al. have expressed concern that the incomplete coverage of MMR in the private sector will result in more young women susceptible to rubella than before, because the natural spread of the virus is inhibited. They provided serological evidence that the immunity gap for rubella in women of childbearing age using private sector health care, was about 11% compared to 5% in those using the public sector health care, and found that only about 60% of MMR doses needed to cover the estimated 100 000 children who had access private health care were distributed in South Africa in 2007 [18]. Vynnycky et al. have expressed similar concerns about the availability of MMR in the private sector [25].

When introducing a vaccine such as MMR, which has caused controversy in a number of countries, Larson et al. have pointed out that good communication about the science, efficacy and safety of vaccines may not alleviate the anxieties many parents have about immunization [26]. Leach and Fairhead argue that often the need is not primarily about providing appropriate information or even the building of trust, but of learning to engage effectively with parents and communities, and to appreciate that such dialogue is more likely to facilitate than constrain efforts to promote the acceptance of vaccines [27].
So the question should really be: when and how should South Africa introduce rubella containing measles vaccine? Schoub et al. have recommended that the introduction be preceded by a targeted programme especially for schoolgirls, supported by sero-surveillance and be repeated annually for at least the 5 years [18]. In South America, where elimination of endogenous measles has been achieved and there is excellent progress on the elimination of endogenous rubella, the Pan American Health Organization (PAHO) recommends a similar approach: (1) starting off with mass campaign of both males and females (the target group depending on the epidemiology of rubella in the country), reaching coverage levels close to 100%; (2) ensuring the highest political commitment and, through intensive social mobilization, and by encouraging full population participation; (3) careful local micro-planning with a practical information system; (4) capacity to detect and rapidly respond to safety and supply concerns and other emerging issues during campaigns [28].

Once measles vaccine coverage over 85% uniformly in all provinces has been verified for a period long enough to be considered sustainable, measles vaccine should be replaced with MMR vaccine in the child hood immunization schedule at 9 and 18 months, preceded by the kind of process shown to be successful in South America.

While efforts to achieve a uniformly high sustained coverage of measles and other vaccines in South Africa should be continued to be enthusiastically implemented, the following actions should be considered:

1. That a surveillance system for congenital rubella syndrome (CRS) is set up in South Africa, along the lines recommended by WHO [29].
2. That the Southern African Development Community (SADC) should continue strengthen measles control efforts so that the Region can, sooner rather than later, move to a strategy to eliminate the endogenous spread of measles and rubella and mumps based on the South American model [28].
3. That the education, information and communication efforts around measles, rubella and mumps be strengthened and sustained, especially the information that families using private sector health care may be more susceptible to congenital rubella—needs to be more clearly and effectively communicated [18,25,28].
4. That consideration should be given to adding a MMR vaccine to the national immunization schedule around entry to high school, regardless whether MMR or measles vaccine was given as an infant [18,23].
5. That tertiary educational institutions where large numbers of young people gather, one dose of MMR vaccine should be strongly encouraged for all students irrespective of immunization history [18,23].

Despite the recent measles epidemic, the goal we set ourselves in South Africa in 1996 to eliminate measles is not that far off. With the new vision to develop a more effective community based primary health care approach, the time does seem right to renew efforts to reach this goal in time to report positively on measles elimination in time for the Millennium Development Goals 2015, and to be well on our way to achieving the same for rubella [30].

Conflict of interest statement

None declared.

References

Review

Immunising the HIV-infected child: A view from sub-Saharan Africa

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ABSTRACT

The HIV-infected children are prone to multitude of infections. In sub-Saharan Africa, HIV/AIDS is certainly an important acquired immunodeficiency and is more likely to negatively impact on immunisation programmes than other forms of immunodeficiencies. Although HIV infection is generally not a contraindication for immunisation, high background HIV prevalence in the region may result in lower rates of vaccine immunogenicity, efficacy and population immunity. Nevertheless, vaccination is still better than natural infection; the risk of vaccination far outweighs the risk of infection with the pathogen. The primary focus of this review is to discuss the lessons learned in vaccinating HIV-infected children particularly with key live-attenuated vaccines in Africa such as Bacille Calmette-Guérin (BCG), measles, oral polio vaccine (OPV), yellow fever and rotavirus. Immunisation against influenza virus, a common cause of respiratory illness, is also discussed as multiple guidelines recommend influenza vaccination for number of groups at high risk such as patients infected with HIV.

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1. Introduction

HIV-infected children are prone to infectious diseases and every effort should be taken to protect such vulnerable populations from vaccine preventable diseases (VPDs). HIV/AIDS is of utmost importance in sub-Saharan Africa and is more likely to negatively impact on immunisation programmes. Although evidence is accumulating that most children from HIV-infected mothers are born HIV-free due to effective mother-to-child transmission (MTCT) programmes in HIV endemic countries, there is still a high rate of MTCT of HIV in the region [1–3]. Globally, HIV affects an estimated 33.2 million (30.6–36.1 million) people and nearly 90% of the 2.5 million children with HIV worldwide are in sub-Saharan Africa [3]. The overwhelming majority of these children are infected through the MTCT [1,2].

With some notable exceptions, vaccines are generally safe and beneficial for immunocompromised persons, although their immunogenicity and effectiveness may be less optimal. The two major issues in vaccinating the immunocompromised include the safety and efficacy of the vaccines [4,5]. Several concerns regarding safety of vaccines have been previously reported [4]. These include adverse events (AEs) or severe adverse events (SAEs) following immunisation especially with live-attenuated vaccines, and in the case of HIV-infected persons, increase in HIV viral load as a result of immune activation and proliferation. Live-attenuated vaccines of concern include Bacille Calmette-Guérin (BCG), oral polio vaccine (OPV), measles-mumps-rubella (MMR), varicella, measles-mumps-rubella-varicella (MMRV) and yellow fever. All inactivated vaccines can be administered safely to persons with altered immunocompetence, whether the vaccine is a killed whole pathogen, recombinant subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine (Table 1). If inactivated vaccines are indicated for persons with altered immunocompetence, the usual doses and schedules are recommended. With respect to efficacy, concerns are often associated with immunogenicity, quality and quantity of antibody titre, duration of protective antibodies, protection against the disease and duration of protection against the disease [4]. Unlike vaccine safety, efficacy is of concern whether vaccination is performed with killed whole pathogen, toxoid, polysaccharide, or polysaccharide protein-conjugate, subunit, or live-attenuated vaccine.

There are number of reasons why HIV-infected children should be vaccinated. In high HIV prevalence regions, the accumulation of susceptible hosts may compromise efforts to control infectious diseases; thus vaccinating HIV-infected children is important in maintaining population herd immunity. Also, HIV damages the immune system and it usually takes a short time for the immune system to be weakened or destroyed; and children are more susceptible to common infections or unusual opportunistic infections (OIs) and progress to AIDS more rapidly. For example, before the era of highly active antiretroviral therapy (HAART), some of the most common OIs among children in the United States were serious bacterial infections (most commonly pneumonia).
Table 1
Summary of recommendations on common vaccines in HIV-infected individuals.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Recommendations</th>
<th>Symptomatic HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Live attenuated</td>
<td>Yes [depends on risk-benefit analysis]</td>
<td>No</td>
</tr>
<tr>
<td>OPV</td>
<td>Live attenuated</td>
<td>Yes [give IPV if available]</td>
<td>No</td>
</tr>
<tr>
<td>Measles</td>
<td>Live attenuated</td>
<td>Yes [vaccinate at 6, then 9 and 18 months]</td>
<td>No</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Live attenuated</td>
<td>Yes [CD4+ &gt; 200 cells/mm³]</td>
<td>No</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Live attenuated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DTPwPDtAP</td>
<td>Inactivated</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IPV</td>
<td>Inactivated</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Inactivated/subunit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>H. influenzae type b</td>
<td>Inactivated/subunit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Inactivated/subunit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Inactivated/subunit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Human papilloma</td>
<td>Inactivated/subunit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

It is important to note that the majority of HIV-infected infants are immunologically normal at the beginning, but in the absence of HAART, they develop progressive HIV infection that leads to the destruction of all aspects of their immune system [4]. This observation is important for continued protection of children against VPDs, taking into account advancing programmes on ARVs, which bring hope to HIV endemic regions by improving the immune status and prolonging survival of most HIV-positive persons. Efforts are underway to improve immunogenicity and efficacy of vaccines in children receiving HAART. It has been noted that those initiating HAART experience immune reconstitution which often improves responses to vaccines and this could be one of the strategies aimed to enhance results of immunisation [11]. On the other hand, immune reconstitution in children is mainly through the generation of naïve T-cells as opposed to the expansion of memory T-cells. It is therefore probable that revaccination may be beneficial in HIV-infected children receiving HAART [12]. Thus, vaccine recommendations for those with HIV infection require continual updating as additional research becomes available.

3. Lessons learned in vaccinating HIV-infected children

Certain live-attenuated vaccines are of major safety concern in HIV-infected persons in that a defective immune system is less able to respond adequately to attenuated vaccine strains, or in rare cases, the vaccine strain may revert to virulence. In both cases, the vaccine strain could multiply to undesirable levels and cause systemic infections with SAEs. With the exception of BCG, asymptomatic HIV-infected children should be immunised according to standard schedules. Thus, the WHO-UNICEF position on vaccination of HIV-infected children supports the routine immunisation of asymptomatic HIV-infected children should be immunised according to standard schedules. Thus, the WHO-UNICEF position on vaccination of HIV-infected children supports the routine immunisation of these children with the exception of BCG and yellow fever vaccines (for asymptomatic HIV infection) [13,14]. Other live-attenuated vaccines such as MMR and varicella should be administered with caution or avoided in symptomatic HIV persons. Some of the new live-attenuated vaccines such as rotavirus have been evaluated and appear to be well tolerated in HIV-infected individuals [15,16].

3.1. BCG in HIV-infected children

BCG is still one of the most widely given vaccines in developing countries and has proven safe in immunocompetent individuals. Recent evidence demonstrated that HIV-infected infants who were routinely given a birth dose of BCG at the time they were asymptomatic, and who later developed AIDS, were at high risk of developing local and disseminated BCG disease (estimated incidence 407–1300 per 100,000) [17,18]. A South African surveillance study reported 32 cases of disseminated BCG over a 3-year period, estimating the risk of disseminated BCG to be 992 per 100,000 vaccinations in HIV-infected children [17]. The AEs and SAEs of BCG in HIV-infected babies include severe inflammation or abscess formation at the site of injection, immobility of the arm, lymphadenopathy, disseminated BCG infection requiring clinical management, death from disseminated BCG infection resulting in multisystem disease. BCG vaccine is not contra-indicated in...
HIV-infected children, its administration should however take into account risk-benefit analysis [13] (Table 1). WHO currently recommends that BCG should not be given in two scenarios: (1) when risks outweigh benefits such as infants who are known to be HIV infected with or without signs, and (2) when risks usually outweigh benefits for infants born to HIV-positive mothers whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection. The latter guideline is applicable only to children who have not yet received BCG in the first few weeks of life, since clinical manifestations typically occur after 3 months of age. Alternatively, BCG vaccination should be delayed until confirmation of HIV status is established usually at 6 months of age [13].

Unfortunately, countries with high prevalence of HIV often have the greatest burden of TB, and uninfected children will benefit from the use of BCG vaccine. There are a number of programmatic challenges in diagnosing and identifying HIV-infected babies around the time (i.e. birth dose) of BCG administration in Africa. Clinical diagnosis is almost impossible in the majority of cases as HIV-infected babies are asymptomatic at birth. Definitive laboratory diagnosis of HIV is based on the detection of the viral nucleic acid by polymerase chain reaction (PCR) assay, a technology which is not always available in many diagnostic centres of the region. The sensitivity of the PCR has also been shown to be low in the first 48 hours of life [19]. The other challenge is that most children from HIV-infected mothers are born HIV-free due to effective PMTCT programmes in HIV endemic countries. For example, a South African PMTCT cross-sectional study designed to assess HIV transmission in infants at their first immunisation visit (4–8 weeks of age) reported a dramatic drop in infant HIV infections to 3.5% [20]. This observation confirms that the majority of infants born to mothers on PMTCT programmes in countries with high burdens of HIV and TB will benefit from the use of BCG as recommended by WHO.

3.2. Measles vaccine in HIV-infected children

Infection with HIV is likely to increase susceptibility and severity of measles infection as HIV infection results in immune suppression and a poor nutritional status. Indeed studies from Zambia have shown that the case fatality rate is higher in HIV-infected children than that in HIV-uninfected children [21,22]. In Zaire (now Democratic Republic of Congo), the case fatality rate was marginally higher in HIV-positive children than in HIV-negative children; however this difference did not reach statistical significance [23]. However, the relationship between the degree of immune suppression due to HIV and severity of measles does not seem to be well established. Vaccinated HIV-infected children have been found to have lower measles antibody levels and they tend to have a more rapid decline in measles antibodies compared with HIV-uninfected children in a number of studies [24–28]. This poorer response to measles vaccination appears to be related to the degree of HIV immune suppression as measured by CD4 counts [29,30]. Conversely, a study conducted among Ugandan children failed to show this association [31].

HIV-infected children are prone to be infected with measles at an earlier age as placental transfer of maternal antibodies including antibodies to measles is impaired [32,33]. These antibodies normally interfere with measles vaccination in infants younger than 9 months; however in HIV-infected children early immunisation may be beneficial as maternal antibodies are likely to be low and HIV-induced immune suppression may not have sufficiently progressed to influence response to immunisation. Accordingly, WHO has recommended that infants at high risk for developing measles before 9 months of age, including HIV-infected asymptomatic infants, should receive measles vaccination at 6 and 9 months of age [34]. Ideally, the vaccine should be offered as early as possible in the course of HIV infection. The vaccine is generally recommended for individuals with moderate immunodeficiency if there is a risk of contracting wild measles from the community. A systematic review of literature on measles vaccination in HIV-infected children suggested that vaccination is safe in these children [35]. Another systematic review reported that from 39 studies that involved >1200 HIV-infected children no deaths related to measles vaccine were observed and only a case of serious adverse event that was possibly related to measles vaccination was noted [36]. Generally, measles vaccine is contra-indicated where there is advanced AIDS. Similarly, MMR or MMRV vaccines can be considered for HIV-infected children who are not severely immunosuppressed (i.e., those with age-specific CD4 cell percentages of ≥15%) [6].

3.3. OPV in HIV-infected children

The use of OPV (Sabin strains) has contributed greatly to the success of polio eradication globally, which was the vaccine of choice for the EPI since 1974 for a number of reasons: affordability and ease of administration, provision of long-term and herd immunity, and superiority to inactivated polio vaccine (IPV) in inducing intestinal mucosal immunity [37]. The efficacy of OPV in HIV-infected children is satisfactory, with over 90% of such vaccines developing protective antibody titres. There has been few reported cases of vaccine-related paralytic polio in Romania [38] and Zimbabwe [39], flaccid paralysis with vaccine polio 2 [38], and paralysis of right leg two weeks post administration of the second dose [39]. In cases with severe immunodeficiency, inactivated polio vaccine (IPV), if available, is a preferred alternative.

The immunocompromised may also be the source of infection following vaccination due to prolonged shedding of the vaccine strain to other immunocompromised susceptibles of the same household. For example, the OPV (Sabin) strains replicate in the human gut and are excreted for several weeks after immunisation in immunocompetent children. This phenomenon may contribute to herd immunity. In a few instances, the excretion could be prolonged in immunodeficient individuals, particularly in severely congenitally humoraly immunodeficient individuals. During excretion period, the mutations associated with attenuation of the vaccine strains can revert. This may, in rare cases, cause vaccine-associated paralytic poliomyelitis (VAPP) in vaccines or result in immunodeficient VDPV (iVDPV) strains which could be excreted for several decades. Outbreaks of poliomyelitis caused by circulating vaccine-derived poliovirus (cVDPV) have recently occurred in communities with long-term incomplete immunisation coverage [40–43].

3.4. Rotavirus vaccine in HIV-infected children

The current rotavirus vaccines comprise live-attenuated viruses. Data on natural rotavirus infection in HIV-infected children demonstrated that there are no major safety or efficacy concerns related to the administration of rotavirus vaccine [15]. Similarly, one study evaluated the safety, reactogenicity, and immunogenicity of Rotarix vaccine in asymptomatic or mildly symptomatic (clinical stages I and II according to WHO classification) HIV-infected South African infants [16]. All symptoms (solicited and unsolicited) occurred at a similar frequency in both groups. Six fatal serious adverse events in the vaccine group and 9 in placebo group were reported. In the vaccine group, satisfactory immune response was elicited without aggravating the immunologic or HIV condition [16]. Thus, rotavirus vaccine appears to be well tolerated in HIV-infected individuals.
3.5. Yellow fever vaccine in HIV-infected children

Yellow fever is a vectorborne disease resulting from the transmission of yellow fever virus to a human from the bite of an infected mosquito, and the disease is endemic to sub-Saharan Africa and tropical South America [44]. It is estimated to cause 200,000 cases of clinical disease and 30,000 deaths annually [44]. There is no treatment for yellow fever disease, thus prevention through vaccination is critical to lower disease risk and mortality. The yellow fever vaccine provides long-lasting immunity [45]. However, rare serious adverse events after vaccination include neurologic or viscerotropic syndromes or anaphylaxis.

WHO recommends that all people aged ≥9 months travelling to or living in areas of South America and Africa in which a risk exists for yellow fever transmission should be vaccinated [13]. However, the vaccine is contraindicated for people who are severely immunocompromised. A recent systematic review of adverse events associated with yellow fever vaccination in vulnerable populations which included nine studies in infants and children as well as nine studies in HIV-infected individuals found yellow fever vaccine to be safe and effective [45]. Only very small numbers of cases of yellow fever vaccine-associated viscerotropic disease, yellow fever vaccine-associated neurotropic disease, and anaphylaxis in persons ≥60 years were identified [45].

To minimise the risk for serious adverse events, yellow fever vaccine is not recommended for symptomatic HIV-positive children [13]. The immunogenicity and safety of yellow fever vaccine in HIV-infected are scarce but show consistent immunogenicity in those with CD4 counts ≥200 cells/mm³ [13]. Published studies in HIV-positive people are limited to small studies and case reports, mainly of travellers with CD4 ≥200 cells/mm³. With the exception of 1 case of fatal meningoencephalitis, these studies did not detect any other serious adverse events among HIV-positive individuals [13].

3.6. Influenza vaccines in HIV-infected individuals

Influenza virus is a common cause of respiratory illness in individuals of all ages with or without HIV co-infection [46,47]. Patients who are immunosuppressed are at risk of serious influenza associated complications. As a result, multiple guidelines recommend influenza vaccination for number of groups at high risk such as patients infected with HIV and those who received either solid-organ transplants, haemopoietic stem-cell transplants, or patients on haemodialysis [47,48]. In addition, a number of health authorities such as CDC and WHO recommend annual influenza vaccination for HIV-infected individuals [49,50]. Influenza is more severe in HIV-infected children as there is an eight-fold greater risk of hospitalisation and death from pneumonia [51]. Children under 6 months of age could benefit from the vaccine on annual basis. Several vaccines are available for seasonal influenza (some also protect against pandemic H1N1). The two main types of influenza vaccines in use include trivalent subunit vaccine which is given intramuscularly and the live-attenuated vaccine which is administered intranasally. The efficacy and effectiveness of both vaccines have shown to be adequate.

Influenza vaccines have been observed to be moderately effective in reducing the incidence of influenza in HIV-infected persons; however, studies in children are limited [52]. Administration of seasonal and pandemic H1N1 vaccines are strongly recommended in HIV-infected adults with CD4 counts above 100 cells/μL or HIV-infected children with CD4 count >15%, although the immunogenicity and efficacy may be sub-optimal [48,50]. Both trivalent subunit and live-attenuated vaccines appear to be safe in stable HIV-infected children (CD4 count >15%) receiving antiretroviral therapy [53]. Nonetheless, concerns about using the live-attenuated vaccine remain and a large number of guidelines suggest that the use of live-attenuated vaccine is contraindicated and recommend that trivalent subunit vaccine should be given instead [54,55]. Finally, there has been some concerns that immunisation with the influenza vaccine leads to transient increases in HIV viral replication and decreases in CD4 cell counts; however, these effects do not seem to be significant [55].

4. Conclusions

Vaccines are generally safe and SAEs are uncommon. All inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole pathogen or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide-protein-conjugate vaccine. If inactivated vaccines are indicated for persons with altered immunocompetence, the usual doses and schedules are recommended. However, the effectiveness of such vaccinations might be suboptimal. Live-attenuated vaccines have potential safety concerns in HIV-infected persons. In this case, the vaccine strain could multiply unrestricted by the immune system and cause systemic disease with SAEs. With the exception of BCG, asymptomatic HIV-infected children should be immunised according to standard schedules. Other live-attenuated vaccines such as yellow fever, measles, MMR and varicella should be administered with caution or avoided in symptomatic HIV persons. It should be noted that the benefits of vaccination in the great majority of cases still far outweighs the risks of vaccination even in the immunocompromised child.

Conflict of interest

None.

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Meeting the need for advocacy, social mobilisation and communication in the introduction of three new vaccines in South Africa – Successes and challenges

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Abstract
Advocacy, social mobilisation and communication are key components of the successful introduction of new vaccines into childhood immunisation schedules. The development of many new vaccines and the innovation of finance mechanisms, means more efficacious vaccines are becoming available to children in developing countries. At the same time, communication technology is developing at a rapid rate, and with the dramatic decrease in vaccine-preventable diseases over the past few decades, the public have become increasingly exposed to confusing and conflicting information about the need for vaccination. The science of vaccines has become more complex, making effective, clear and consistent communication for healthcare workers and caregivers critical to the uptake of and adherence to lifesaving vaccination. The introduction of two new vaccines, the 7-valent pneumococcal conjugate vaccine and the rotavirus vaccine together with the new pentavalent vaccine, which includes inactivated polio vaccine and replaced the former combination vaccine with four antigens, into the South African Expanded Programme on Immunisation over a short period of time, has been met with a number of challenges, some of which led to a lowering of confidence in the Department of Health to deliver on its promises. Had consistent advocacy, social mobilisation and communication efforts not been in place, efforts to make an impact on the burden of disease may not have been as successful. This paper focuses on the lessons learned about effective advocacy with decision makers, social mobilisation, communication with parents and caregivers, and training healthcare workers regarding the introduction of the new vaccines.

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1. Introduction

Immunisation has moved to centre stage as one of the driving forces behind efforts to meet the millennium development goals (MDGs) – especially goal 4 which aims to reduce the under 5 years of age mortality rate (U5MR) [1].

Although worldwide mortality in children younger than 5 years has dropped from 11.9 million deaths in 1990 to 7.7 million deaths in 2010, almost half of these deaths (49.6%) occur in sub-Saharan Africa [2]. In 1990, South Africa’s U5MR was estimated at 62 per 1000 live births, but mainly because of a failure to prevent maternal to child transmission of human immunodeficiency virus (HIV), by 2002 it had risen to above 80 per 1000. By 2009 the U5MR had dropped back to 62, which while encouraging, makes it particularly challenging for South Africa to reach the MDG target of 20 per 1000 by 2015 [3].

In developing countries, more vaccines have become available and more lives are being saved. For the first time in documented history the number of children dying every year has fallen below 10 million – the result of improved access to clean water and sanitation, increased immunisation coverage, and the integrated delivery of essential health interventions [1]. More funding is available for vaccines and new vaccines have been developed with others in the late stages of clinical trials, making this decade the most productive in the history of vaccine advancement. Significantly, pneumococcal and rotavirus vaccines are now also...
available to Global Alliance for Vaccines and Immunisation (GAVI) – eligible countries, preventing a large fraction of two of the leading causes of child mortality – pneumonia and diarrhoea. Their introduction provides an opportunity to scale up interventions for the prevention and treatment of pneumonia and diarrhoea to achieve better overall disease control [1].

2. Vaccine introduction in South Africa

South Africa is a middle income country and does not qualify for GAVI assistance. However, in its quest to turn the tide on childhood morbidity and mortality, it has stepped up to the mark, initially introducing the 7-valent pneumococcal conjugate vaccine (PCV7) and then rotavirus vaccine (RV) into the Expanded Programme on Immunisation of South Africa (EPI-SA) within a year (between 2008 and 2009).

It was the first country in Africa to do so, in its push to achieve MDG 4, while addressing the World Health Organization’s (WHO) Global Immunisation Vision and Strategy (GIVS) to introduce a range of newly available vaccines and technologies [4].

The pentavalent vaccine (diphtheria, tetanus, acellular pertussis, inactivated polio, and Haemophilus influenzae type b (DTaP-IPV/Hib)) was also introduced at the same time during 2008–2009. This replaced the former four-antigen vaccine, diphtheria, tetanus, whole cell pertussis and H. influenzae type b (DTWP-Hib). The introduction of these vaccines was no easy feat for a country with nine provinces, 52 districts and more than 3500 health facilities, including those in remote areas. To its credit South Africa, using its own resources, was also the first country on the African continent to have introduced H. influenzae type b vaccine into the primary childhood immunisation schedule in 1999 [5] and among the first three to launch hepatitis B vaccine on the continent in 1995 [6].

3. Advocacy and communication

Advocacy and communication together comprise one of the five operational components of any immunisation system and need to be part of plans for the successful introduction of new vaccines. The other four components for a healthy immunisation system listed by the WHO, are (a) vaccine supply and quality, (b) logistics and cold chain, (c) service delivery and (d) surveillance and data [7]. The three basic elements of the immunisation system are adequate management, sustainable financing and strengthening of human and institutional resources, including teaching and training of healthcare workers (HCWs).

The WHO guidelines on the introduction of new vaccines, advises that advocacy begins at the start of the decision-making process to ensure that funding is made available and political commitment is provided for the new vaccines. According to these guidelines, advocacy is best characterised as any effort to influence policy and decision-makers, to fight for social change, to transform public perceptions and attitudes, to modify behaviour, or to mobilise human and financial resources [8].

There are several steps to take in order to conduct an effective advocacy and communication effort namely: (i) gathering information; (ii) building a plan; (iii) creating messages and material; (iv) building a strong coalition; (v) engaging policy and decision-makers; (vi) informing and involving the public; (vii) working with mass media; and (viii) monitoring and evaluation. With foresight, and in spite of the enormous challenges, these guidelines were followed by the EPI-SA.

4. Burden of disease and advocacy

The rigorous decision-making process goes through at least four protracted stages [9]. Against a high background rate of HIV/AIDS, tuberculosis and elevated child mortality from diarrhoea and pneumonia, the EPI-SA and the ministerial committee, the National Advisory Group on Immunisation (NAGI), began advocating for the introduction of PCV7 (which was available at the time) and RV. In February 2008, the EPI-SA recommended to the former Minister of Health (MoH) that PCV7 be introduced by 2010, allowing a 2-year gap for proper planning. The recommendation for a DTaP-IPV/Hib vaccine, the switch-over from DTWP-Hib, had already been submitted in 2007. All submissions were based on the epidemiology of the diseases, and the efficacy and cost-effectiveness of the vaccines. The NAGI recommendations to the South African Department of Health (SA-DoH) supported the WHO position papers on the introduction of PCV7 and RV vaccines, and the switch from oral polio vaccine to IPV [10,11].

5. Political commitment

In April 2008 there was a spike in child deaths in the rural Ukhahlamba District of Eastern Cape Province, with 70% of 140 deaths reportedly due to gastroenteritis, pneumonia and malnutrition. Rather than any specific disease outbreak, the deaths were mainly attributable to weaknesses in the health system [12]. Widespread media coverage prompted the MoH to travel to the area on the border of Lesotho to attend to the crisis and offer support. Propelled by the Ukhahlamba deaths, public concern and advocacy efforts to get government to financially and politically commit to the introduction of the vaccines, the MoH announced to the 61st World Health Assembly in May 2008 in Geneva, that the vaccines against pneumococcal and rotavirus disease would be introduced within 3 months [13]. Instead of a 2-year lead in, the plan had to be fast-tracked to meet the deadlines and this had huge financial and programmatic implications as both vaccines would be introduced sooner and simultaneously with the new pentavalent vaccine.

6. Social mobilisation and cold chain capacity

It was decided that the vaccines would be introduced to coincide with the new health budget announced in April 2008 and to be implemented in 2009. Apart from financing issues, it was acknowledged that training and social mobilisation, as well as cold chain capacity had to be assessed and strengthened before the vaccines could be introduced. Social mobilisation is a process of gaining and sustaining the involvement of all stakeholders to take action or to attain a common goal [14] – in this case the immunisation of children with three new life-saving vaccines. The audits of all primary healthcare facilities were submitted as part of the tender process and the companies built in funds for training, social mobilisation and refrigerator capacity (which had to increase by over 450%).

The national health promotion team submitted a plan to the MoH requesting finance for the design and printing of promotional material. With the assistance of the vaccine manufacturers, the EPI-SA schedule was updated and reprinted to include the new vaccines without disrupting the existing 6, 10, 14 weeks and 9 month clinic visit as well as the existing 18 month visit with regard to DTaP-IPV/Hib, thus ensuring greater adherence and acceptability of the vaccines. Posters of the new schedule were designed, printed and distributed.

Underscoring government support and in the interests of national social mobilisation, it was agreed the MoH would be present at the national launch of the PCV7 and RV vaccines in the Eastern Cape, and it was planned that the heads of health of each of the nine provinces would be involved in the launch in their
areas of jurisdiction. A communication task team was formed which involved relevant stakeholders including WHO representatives, national EPI, national Health Promotion and Communications, the Public Private Partnership (PPP) – in which the government has a 51% stake, and which procures the vaccines on behalf of the SA-DoH – and the three vaccine companies which were awarded tenders for the supply of the new vaccines.

7. Communication plan

Following WHO guidelines, a communication plan was developed with the objectives, target audiences, activities, messages and indicators, channels of communication, time frames and budget laid out for the national roll-out of the vaccines.

8. Training of HCWs

Initial training of HCWs was conducted with the assistance of the vaccine companies and the PPP in the Eastern Cape’s Ukahlamba District from 25 to 28 August 2008. Thereafter training of HCWs was rolled out countrywide with two sessions in each of the nine provinces with representatives from every district. The trainees were instructed to cascade the training to all HCWs in primary healthcare clinics before implementation. All the aspects of the new vaccines were communicated to HCWs including: what they are indicated for, the disease burden, efficacy, schedules, delivery routes, dosages, the potential side effects and possible adverse events following immunisation (AEFIs), procurement, ordering, vaccine management, and risk benefit communications as well as how to communicate in the event of any AEFIs.

9. Communication materials, channels and tools

The national EPI collated materials with the financial and logistical assistance from the vaccine companies. These materials, including brochures and posters, which had to be translated into the various languages were printed and delivered to all the facilities. Varied communication channels were used to ensure wide publicity. These included: the print (local, regional and national newspapers, journals, women and baby magazines) and electronic media (local and national radio, television and internet). Various tools were used to reach the media including press releases, fact sheets, media scripts, advertorials in newspapers and magazines, radio adverts, consumer pamphlets (Fig. 1), loud hailers, community road shows (edu-mobiles) and banners (Fig. 2) were used to get the pro-immunisation messages across and to answer the public’s questions and concerns about the introduction of the new vaccines. Paediatricians in the private sector as well as health scientists were reached via journal articles and meetings.

An example of one of the radio jingles aired on national and regional radio is as follows:

**Man’s voice:** Pneumococcal diseases such as pneumococcal meningitis, pneumonia, ear and blood infections can be harmful to your baby.

**Woman’s voice:** When your baby is 6-weeks old go to your local clinic and ask about pneumococcal vaccination to help protect your baby.

**Child’s voice:** All we want to do is to grow up happy. Don’t Wait. Vaccinate!

**Man’s voice:** A national immunisation programme brought to you by the Department of Health supported by (the name of a pharmaceutical company supplied).
Although the vaccine companies contributed to the design and the wording of various promotional materials, the SA-DoH conducted the campaign with consistent messages about both the risks and benefits of the vaccines. Messages included that:

- **Vaccination is the most cost-effective medical intervention to date.**
- **All medicines have side effects, and while vaccines can have adverse events these are mostly mild local reactions and temperature peaks indicating an immune response.**
- **Serious or fatal reactions from vaccines are extremely rare, much rarer than the incidence of vaccine-preventable diseases.**
- **The benefits of vaccinations far outweigh the risk of adverse events. When considering a vaccination for ourselves or our children, it is natural to think about the potential negative effects of that vaccination. But you have to balance the risk against the benefits.**
- **Vaccination is different from giving medicine to an ill child to make them better. Vaccinations protect children against serious illness.**
- **Deciding not to vaccinate your child puts them at risk of catching a range of potentially serious, even fatal, diseases.**
- **In reality, having a vaccination is much safer than not having one. They are not 100% effective in every child, but they are the best defence against epidemics that can potentially kill or permanently disable millions of children and adults.**
- **All vaccine companies have put their vaccines through randomised clinical trials, to test for safety and effectiveness before they can be registered for use.**
- **All vaccine company trials are subjected to ethical review.**
- **All vaccine companies have to include possible or expected AEFIs with their product insert.**

### 10. Vaccine launch

The MoH duly launched the PCV7 and RV at Upper Telle village, in the Senqu sub-district of Ukhahlamba on 12 September 2008 with local, national and international coverage from the media, all of whom had been invited [15]. Upper Telle village was selected for the launch because it is part of the Ukhahlamba District where there had been numerous deaths reportedly due to gastroenteritis, pneumonia and malnutrition. The MoH also wanted to show political support and the SA-DoH’s commitment to reaching people, irrespective of where they live and the challenges they face. Upper Telle is difficult to access, situated in a remote, mountainous area on the border with Lesotho and the Free State Province. The Upper Telle clinic staff are also under enormous pressure, having to deal with cross-border clients as well as locals who are mostly poor. Bisected by a river from Lesotho, the area has water and sanitation challenges.

After the launch, the vaccines were rolled out district-by-district in the Eastern Cape until the planned countrywide introduction in April 2009.

Build-up activities for community mobilisation were held in Upper Telle Village in the week before the launch. A team of health officials, community HCWs and volunteers conducted a door-to-door campaign in the sub-district to inform community members about the launch. Schools and community meetings were held to communicate vaccine messages including catchy phrases such as: Don’t wait. Vaccinate! The vaccine companies sponsored EPI-branded marketing materials for learners and the community, including school bags, lunch boxes, squeeze bottles, stationery, sun hats, T-shirts and warm hats.

The dirt road was levelled, improving access to the village, and the MoH accompanied by officials joined other stakeholders including traditional healers and local leaders in the launch programme. This included child dancers and praise singers. As a sign of solidarity the MoH participated in vaccinating the children (Fig. 3). Mothers and caregivers could weigh their babies and receive other services at the launch.

### 11. Vaccine product change

The intended simultaneous roll-out of RV together with PCV7 nationally never materialised due to unforeseen challenges. PCV7 and lyophilised RV were rolled out in the Eastern Cape Province by March 2009 with PCV7 being introduced countrywide by April 2009. The manufacturer of the RV vaccine decided to switch production to the fully liquid vaccine, which needed to be registered by the national drug regulatory authority, the Medicines Control Council, and this effectively delayed the national implementation of RV to 1 August 2009. One province rolled out both vaccines only in October 2009, due to severe financial constraints.
12. Communication restores confidence

The deferred introduction of RV vaccine gave HCWs a welcome gap to deal with teething problems around the PCV7 vaccine roll out, and also helped ease budget constraints in the first year. However, the delay had a negative impact on community expectations. Extensive and sustained social mobilisation and communication created interest and demand for the vaccine so when caregivers arrived at the facilities expecting the vaccine, they became angry and upset that it was not available. Reassurance had to be given to the public and confidence and trust in the government and EPI-SA had to be restored.

13. Stock out challenges

Widespread stock outs of all three vaccines at various stages in various provinces also affected public confidence in the SA-DoH’s promise to deliver. The vaccine shortages were negatively presented in the media in Limpopo Province, for example, where it was reported that there were no RVs in the public sector although the private sector was well stocked. The headline of the article read: Rotavirus Outcry: No vaccine in Limpopo Public Hospitals.

Poor communication led to delays. So, while the facilities were expecting stocks to arrive, the depots were waiting for the facilities to place their orders. In addition, some provincial and district depots had to handle large stocks and because some provinces had not strengthened their cold chain capacity before implementation, there was limited capacity to order and store vaccines from the manufacturers. This resulted in the need for more frequent ordering to be able to meet the demand for the now eagerly awaited vaccines at the facilities.

14. Anti-vaccination lobby

Although the anti-vaccination lobby is continually active, there were no serious threats to the roll-out from this group. Before the introduction, HCWs in some provinces raised concern that three injections administered at one visit would be met with opposition from parents. These fears were largely allayed with appropriate inter-personal communication between HCWs and the caregivers.

15. Training and personnel capacity building

Training and capacity building of personnel and adapting data collection systems was challenging across the 52 districts and the more than 3500 facilities. The new Road to Health Card (RTHC) used by HCWs to keep a record of the child’s vaccination status only came into circulation in March 2011. Until then, vaccinators were instructed to record the pentavalent vaccine in the DTP space on the old RTHC, write “Pentaxim” (the DTaP-IPV/Hib vaccine) in the DTP space, and record PCV7 in the Hib space on the old card (Fig. 4). In addition to data capturing challenges, the health facilities were overstretched with the competing priorities of rendering a comprehensive service. The global financial crisis had by that stage hit South Africa and the moratorium on posts at national and provincial level meant that existing staff had to carry the additional burden. Pharmaceutical services were particularly under pressure with pharmacists leaving the public service and others emigrating, resulting in a scarcity of skills in this area. Personnel shortages affected supportive supervision, monitoring and evaluation of the introduction of new vaccines.

16. Conclusion

The introduction of new vaccines affects many aspects of the healthcare system, including service delivery policies and vaccine procurement and logistics. Changes in any of these areas can impact communication strategies and messages [16]. This is why it is essential to plan communication about new vaccines far in advance of their introduction. The MoH’s decision to introduce three new vaccines (PCV7, RV and pentavalent) in 1 year put enormous strain on finances and the overall healthcare system. Communications and social mobilisation were put to the test. The assistance of the vaccine companies in devising, printing and distributing appropriately targeted and translated material, helped to relieve the under-funded and over-burdened health promotions staff at national and provincial level.

Sustained advocacy efforts by the EPI-SA and the NAGI successfully influenced policy makers and politicians at the highest level. In addition, the MoH had great foresight in making the important decision to introduce the vaccines, which was ultimately reflected positively in the media. The launch at Upper Telle proved successful, with the event receiving the local and international attention that was planned for.

The hallmark of good communication planning is to be prepared and plan for misinformation, confusion and negative reactions when introducing something new into the healthcare system. People are often resistant to change and it takes time to win over “late acceptors” and to respond to the questions and concerns of all relevant staff [16]. The delay in rolling out RV due to a change in the product and the need to have it registered and the stock-outs left caregivers disappointed, HCWs frustrated and caused some negative publicity. However with communication and clear consistent messages, public confidence was restored.

Parents report that their most reliable source of information is the HCW [17] which puts the onus on the SA-DoH to ensure HCWs
are up to speed with information about the new vaccines, that they are well versed in risk benefit communication, that they are able to answer all caregiver’s questions in a clear and consistent manner and that their interpersonal communication skills are such that they do not alienate the caregiver. The SA-DoH prioritised training of HCWs in all districts to equip them with these skills, but without the financial backing and assistance of the vaccine companies they may not have reached as many HCWs in the time required. The moratorium on posts and the lack of skills in specific areas such as pharmacy services, was not ideal at a time of great pressure and added to the challenges faced by HCWs.

In spite of the challenges, the SA-DoH needs to be congratulated, as the three vaccines were successfully advocated for, accepted by the target audience, who through successful social mobilisation, communication and information were willing to take up the vaccine in a relatively short period of time across the entire country. This is evidenced by the fact that in 2009, eight of the nine provinces had at least 80% coverage of fully vaccinated 1-year-olds [18].

Lessons learned include: ensuring that there is secure, sustainable financing and that human resources are strengthened; that project management principles are crucial for introducing new vaccines; planning takes time; introducing new vaccines must strengthen the immunisation programme, not weaken it; and that one new vaccine be added at a time, unless adequate time and capacity is allocated for the introduction of more than one.

Conflict of interest statement

None declared.

References


Addressing public questioning and concerns about vaccination in South Africa: A guide for healthcare workers

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1. Introduction

Vaccination is one of the most cost-effective and successful public health interventions in the history of mankind. Anecdotal evidence, the media, and South African-based anti-vaccination websites and blogs point to the existence of anti-vaccination lobbies in South Africa, although the part played by these lobbies in sub-optimal vaccination coverage is unknown at present. This article discusses some of the claims made by South African anti-vaccination groups, including some drawn from anti-vaccination lobbyists based in highly resourced countries. While research is underway to better understand the scope and influence of anti-vaccine groups, it is important to build capacity among healthcare workers within the Expanded Programme on Immunisation of South Africa to enable them to deal empathically and effectively with parents and caregivers who have been exposed to anti-vaccination messages and who question the need to vaccinate their children. Claims that vaccines cause adverse effects need to be supported by valid and reliable scientific evidence. However, evidence alone that vaccines are safe and effective does not always result in parents being convinced to vaccinate their children. In addition to providing important evidence of vaccine safety, this paper discusses the important role of communication – especially dialogue – in building public trust in vaccination with the ultimate goal of increasing vaccination coverage and preventing future outbreaks of vaccine-preventable diseases.

Abbreviations: AEFI, adverse event following immunisation; DTaP, diphtheria, tetanus, acellular pertussis vaccine; EPI-SA, Expanded Programme on Immunisation of South Africa; HICW, healthcare worker; Hib, Haemophilus influenzae type b vaccine; IPV, inactivated polio vaccine; MMR, measles, mumps, rubella vaccine; MSVs, multiple simultaneous vaccines; NAGI, National Advisory Group on Immunisation; NITAG, National Immunization Technical Advisory Group; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine; RCT, randomised clinical trial; VPD, vaccine-preventable disease; WHO, World Health Organization.

Addressing public questioning and concerns about vaccination in South Africa: A guide for healthcare workers

Review

Vaccination for the prevention and control of infectious diseases is one of the most cost-effective and successful public health interventions in the history of mankind. Anecdotal evidence, the media, and South African-based anti-vaccination websites and blogs point to the existence of anti-vaccination lobbies in South Africa, although the part played by these lobbies in sub-optimal vaccination coverage is unknown at present. This article discusses some of the claims made by South African anti-vaccination groups, including some drawn from anti-vaccination lobbyists based in highly resourced countries. While research is underway to better understand the scope and influence of anti-vaccine groups, it is important to build capacity among healthcare workers within the Expanded Programme on Immunisation of South Africa to enable them to deal empathically and effectively with parents and caregivers who have been exposed to anti-vaccination messages and who question the need to vaccinate their children. Claims that vaccines cause adverse effects need to be supported by valid and reliable scientific evidence. However, evidence alone that vaccines are safe and effective does not always result in parents being convinced to vaccinate their children. In addition to providing important evidence of vaccine safety, this paper discusses the important role of communication – especially dialogue – in building public trust in vaccination with the ultimate goal of increasing vaccination coverage and preventing future outbreaks of vaccine-preventable diseases.

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2. Vaccination coverage and anti-vaccination opinion in South Africa

The EPI of South Africa (EPI-SA) has made considerable progress in the past 16 years, and currently eight of the nine provinces have at least 80% coverage of fully vaccinated one-year-olds [9]. This includes a birth dose of both oral polio vaccine (OPV) and Bacille Calmette Guérin (BCG); a further dose of OPV at 6 weeks; rotavirus vaccine (RV) at 6 and 14 weeks; both hepatitis B (Hep B) and a pentavalent (diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type b) vaccine (DTaP-IPV/Hib) at weeks 6, 10 and 14; pneumococcal conjugate vaccine (PCV13) at weeks 6 and 14; and both PCV13 and the first dose of measles vaccine at 9 months [10]. However, when these aggregate data are unpacked, it is clear that vaccination coverage remains sub-optimal in several districts and sub-districts, with 12 of the 52 districts having less than 80% coverage, three of which having coverage of less than 70%. Of particular concern is that six sub-districts did not achieve 80% first dose measles coverage, with two sub-districts in the Eastern Cape achieving only 49.2% and 56.2% coverage. Even more concerning is the second dose measles vaccination (administered at 18 months) drop-out rate, with the provincial drop-out rate ranging from 12% to 21.4%, and six districts having drop-out rates in excess of 20%, with one district in Gauteng Province having a drop-out rate of 28.4%. The worst performing sub-district was in the Eastern Cape, with a drop-out rate of 61.6% [9]. Sub-optimal measles vaccination coverage in South Africa led to a recent measles outbreak, which started in the highly urbanised Gauteng Province, the economic hub of the country, and then spread to all nine provinces, with 5860 confirmed cases in 2009, and 12 499 in 2010 [11]. While many factors may contribute to pockets of low coverage in the country (e.g., missed vaccination opportunities; incorrect information given by clinic staff; unavailability of vaccines; and lack of access to clinics [12]), the part played by the anti-vaccination lobbies in South Africa is as yet unexplored.

Anecdotal evidence, the media, and South African-based anti-vaccination websites and blogs point to the existence of such lobbies in South Africa, which seem to be of two broad types: (1) affluent, relatively educated, mainly white individuals, including homeopaths, dentists, paediatricians, nurses, and their clients, who use mass media including radio, TV, newspapers, popular magazines, websites and Internet blogs to communicate misinformation about vaccines; and (2) poor, relatively uneducated, mainly black, religious/cultural/traditional groups who do not use mass media. However, very little is known about the extent, characteristics, and influence of these anti-vaccination lobbies in South Africa. Thus research is currently underway to gain a better understanding of what the anti-vaccination concerns are and what is driving them, with the ultimate aim of developing interventions to increase public confidence in vaccines and as a result to increase vaccination coverage in the country [3]. In the interim, it is important to build capacity among healthcare workers (HCWs) to enable them to deal empathically and effectively with parents/caregivers who have been exposed to anti-vaccination messages and question the need to vaccinate their children.

3. Study designs to prove causation

Claims that vaccines cause adverse effects need to be supported by valid and reliable scientific evidence. Immunisation programmes in most countries address vaccine safety, including surveillance of adverse events following immunisation (AEFIs) as a major component of their programmes [1,2].

Characterisation of AEFIs, referred to as safety assessments, should follow standard case definitions drawn up by the Brighton Collaboration, the world’s largest network of vaccine safety experts [13]. This allows for the collection of valid comparable data across many multinational sites both during pre-licensure randomised clinical trials (RCTs) and post-licensure studies [14]. Recently the size of Phase III RCTs (the final phase RCT before licensing, which tests both vaccine safety and efficacy on a large statistically powerful number of volunteers) has been increased even further to allow for the detection of very rare AEFIs. For example, the second generation rotavirus vaccines were tested on 60 000 infants in order to detect if there was an association with intussusception, which had previously been shown to have an attributable risk of 1 in 10 000 vaccinees in the post-licensure evaluation of RotaShield® [14].

Since very rare AEFIs may not have been detected during pre-licensure Phase III RCTs, post-licensure evaluations are conducted on an on-going basis. These evaluations cannot be conducted using an experimental design, thus observational study designs must be utilised instead. See Table 1 for the data needed from observational studies to establish a link between an AEFI and a particular vaccine or vaccine combination.

4. Anti-vaccination claims in South Africa and evidence to refute them

A recent unpublished study on South African-based websites and Internet blogs found that South African Internet-based anti-vaccination lobbyists are very much influenced by mass media reports from around the world. Most either have links to anti-vaccination websites from highly resourced countries [15–17] such as the United States of America (USA) which has been documented to have the most anti-vaccination sites on the world-wide web [18,19], or cite anti-vaccination claims from these countries [15,20,21]. Previous global studies have identified the claims on the world-wide web discussed below [18,19,22–25]. Interestingly, none of these previous studies identified South African-based anti-vaccination websites, thus clearly South Africa is still in the process of catching up with global trends regarding Internet-based anti-vaccination lobbying. The claims that are irrelevant to the South African context and are thus easy for South African HCWs to refute are not discussed here, including mandatory vaccination and the cost of vaccination. In South Africa, vaccination is not mandatory, and healthcare, which includes vaccination, is offered free of charge to pregnant women and under six year-olds at all clinics throughout the country [26].

- “Vaccines are not safe and cause disease”

Some of the South African anti-vaccination messages on the Internet give the overall impression that vaccines in general cause disease [15,16], with some messages targeting specific vaccines or constituents of vaccines as discussed below.

“The measles, mumps, rubella vaccine (MMR) causes autism”

While there have been claims that vaccines cause disease from the time when vaccines were first introduced to the world in the late 18th century, a more recent anti-vaccination movement arose after a 1998 publication in The Lancet by Wakefield et al. that linked MMR to autism [27]. Mass media reports that followed in the United Kingdom (UK) led to MMR coverage dropping in the...
UK from 91% in 1997, to 82% in 2004 [28], with one study from Bromley reporting only 60% coverage in 2003 [29].

The Wakefield study was extremely small (twelve children, eight of whom it was claimed had developed autism shortly after being vaccinated with MMR), there was no comparison group, temporal sequence could not be established in most cases, and the causal mechanism was not biologically plausible [30]. Many very large (populations ranging from hundreds to more than one million) ethically conducted epidemiological studies found no association between MMR and autism [31–44] (see Table 2).

Unfortunately while the mass media were quick to spread the news of the original Wakefield paper and his additional claims in a press conference [3], they have been relatively silent on the ensuing studies refuting his findings.

Despite this claim being fully refuted [14,30], with 10 of Wakefield’s 12 co-authors retracting the interpretation of the findings [45], and the withdrawal of the article by The Lancet in 2010 [46] with the author being erased from the medical register by the UK General Medical Council [47], the repercussions are still being experienced today – including in South Africa. These include anecdotal reports of parents refusing to sign informed consent for their children to be vaccinated in the mass immunisation campaigns held during the recent measles outbreak, and anecdotal evidence from HCWs deployed in these campaigns points to fear of the measles vaccine causing autism (although the MMR is not used in the EPI-SA, it seems many people associate the measles vaccine, and sometimes vaccines in general, with autism) being one of the reasons behind this refusal. The claim that vaccines in general cause autism can also be found on some South African websites and Internet blogs [16,21], with links to websites based in highly resourced countries [16].

“Thimerosal (thimerosal) causes autism”

Another common anti-vaccination claim that has been fully refuted [14,30], is that thimerosal, a mercury-based preservative (ethyl mercury) that is used in some multi-dose vaccines, causes autism [1–3,14,28,30]. Thimerosal (sometimes referred to simply as mercury on these websites) is among a long list of “toxins” cited on South African anti-vaccination websites [16,20,21] that are “poisoning” vaccinated children and causing a myriad of diseases, as reported elsewhere [22,24,25]. As with the MMR claim, there is some confusion about what it is in vaccines that supposedly causes autism, with one author erroneously stating that the MMR vaccine contained “a mercury-based preservative” believed by some parents to have caused autism in their children [17]. In fact no preservatives are used in MMR since it is a live vaccine – thimerosal would inactivate the vaccine and render it useless [30].

Vaccines that contain thimerosal do not contain the element mercury as such, just as table salt does not contain the very toxic elements sodium and chlorine as such. However, in 1999, it was recommended by the American Academy of Pediatrics and Public Health Service that, as a precaution, thimerosal should be removed from infant vaccines. This was because there was scientific uncertainty about the effects of ethyl mercury, and most of the infant vaccines contained thimerosal at that time. The concern was that 6-month-old infants could already have received as much as 187.5 μg of ethyl mercury through vaccinations, which exceeded the USA government limit allowed for methyl mercury [14]. Ethyl and methyl mercury are very different types of mercury compounds, with ethyl mercury being processed and excreted by the body more rapidly than methyl mercury [48]. Methyl mercury occurs naturally in the environment, in water, breast milk, infant formula, etc. [14]. Before thimerosal was removed from most infant vaccines in the USA, more than twice the amount of mercury contained in these vaccines as ethyl mercury, was ingested in the form of methyl mercury by an exclusively breast-fed baby in the first 6 months of life [14].

Instead of welcoming this precaution to limit the exposure of babies to mercury, the anti-vaccination lobby took advantage of the situation and reacted by linking thimerosal to autism [1,30]. There is however no evidence to support any link between thimerosal and autism, and mercury as a cause of autism is biologically implausible, since the signs and symptoms of mercury poisoning are clinically very different from those of autism [14,30]. In fact, many very large (up to 467 450 children) studies have shown no link whatsoever [44,49–54] (see Table 3). Also, the USA has not seen a concomitant drop in autism cases since thimerosal was removed from infant vaccines in 1999 [3].

“Multiple simultaneous vaccines (MSVs) cause chronic disease”

It has also been hypothesised that receiving too many vaccines overwhelms the immature immune system and causes chronic diseases, including autism, all of which have been fully refuted [14,30]. Similar claims are seen on South African websites, including an electronic newspaper interview of a homeopath who believes that vaccines are immunosuppressive [55], and an anti-vaccination website authored by a medical doctor who believes that vaccines cause immune overload, destroying the immune system and causing many diseases and death [16]. This claim seems to be based on a belief that natural disease builds immunity while vaccines destroy immunity [19,22–25]. In fact, a vaccine acts very much like a natural infection – without causing infection – since it contains the same (or similar) antigens as the causative organism that elicits the immune response from the host.

There is no evidence supporting any link between MSVs and autism, or that MSVs weaken the immune system leading to the development of other chronic diseases, or that MSVs cause more severe AEFIs [30,56]. While the number of vaccines that infants receive has increased over the last 30 years, due to improved technology the immunologic load has decreased and not increased. For example, in the USA in 2009, fourteen vaccines delivered <200 antigens, compared to 1980, when seven vaccines delivered >3000 antigens [30]. The whole-cell pertussis vaccine that was introduced in 1926 contained about 3000 antigens and was thus responsible for most of the antigenic load, whereas the acellular pertussis vaccine introduced in 1991 contains only 2–5 antigens [14]. In addition, children are exposed to many foreign antigens every day through ingesting bacteria along with the food they eat and interacting with their environment, and they also get a number of bacterial and viral infections every year [30,56]. Also, unvaccinated and vaccinated children respond to non-vaccine preventable infections in the same way, which illustrates that vaccination does not weaken the immune system [30]. Finally, autism is not an immune-mediated disease, thus it is not biologically plausible that an inappropriate immune response from a weakened or over-stimulated immune system could cause autism [30].

• “Vaccines are ineffective”

The notion that vaccines are ineffective is often based on the perception that the majority of people who get the disease have been vaccinated. In countries where vaccine coverage is high, this may well be the case, because no vaccine is 100% effective, with most being 85–95% effective [56]. The WHO provides an excellent hypothetical example of a high school with 1000 pupils who have never been exposed to measles to illustrate this phenomenon. Of the 1000 children, 995 are fully vaccinated against measles, and all 1000 are exposed to measles. Of the 5 unvaccinated children,
Table 2

Studies showing no link between MMR and autism.

<table>
<thead>
<tr>
<th>References</th>
<th>Number of subjects</th>
<th>Study design</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peltola et al. [31]</td>
<td>~1 500 000 (0)³</td>
<td>Prospective cohort</td>
<td>Finland</td>
</tr>
<tr>
<td>Taylor et al. [32]</td>
<td>498 (498)</td>
<td>Case series</td>
<td>UK</td>
</tr>
<tr>
<td>Patja et al. [33]</td>
<td>1 800 000 (0)</td>
<td>Prospective cohort</td>
<td>Finland</td>
</tr>
<tr>
<td>Farrington et al. [34]</td>
<td>357 (357)</td>
<td>Case series</td>
<td>UK</td>
</tr>
<tr>
<td>Kaye et al. [35]</td>
<td>305 (305)</td>
<td>Ecological</td>
<td>UK</td>
</tr>
<tr>
<td>Dales et al. [36]</td>
<td>Not available¹</td>
<td>Ecological</td>
<td>USA</td>
</tr>
<tr>
<td>DeWilde et al. [37]</td>
<td>355 (71)</td>
<td>Case control</td>
<td>UK</td>
</tr>
<tr>
<td>Fombonne and Chakrabarti [38]</td>
<td>272 (272)</td>
<td>Ecological</td>
<td>UK</td>
</tr>
<tr>
<td>Taylor et al. [39]</td>
<td>473 (473)</td>
<td>Case series</td>
<td>UK</td>
</tr>
<tr>
<td>Mäkelä et al. [40]</td>
<td>535 544 (352)</td>
<td>Retrospective cohort</td>
<td>Finland</td>
</tr>
<tr>
<td>Madsen et al. [41]</td>
<td>537 303 (738)</td>
<td>Retrospective cohort</td>
<td>Denmark</td>
</tr>
<tr>
<td>DeStefano et al. [42]</td>
<td>2448 (624)</td>
<td>Case control</td>
<td>USA</td>
</tr>
<tr>
<td>Sneth et al. [43]</td>
<td>5763 (1294)</td>
<td>Case control</td>
<td>UK</td>
</tr>
<tr>
<td>Fombonne et al. [44]</td>
<td>27 749 (61)</td>
<td>Ecological</td>
<td>Canada</td>
</tr>
</tbody>
</table>

Source: Based on Amanna and Slifka [28] and Gerber and Offit [30].

¹ Number of autism cases in parentheses.

³ 3 million doses.

Table 3

Studies showing no link between thimerosal and autism.

<table>
<thead>
<tr>
<th>References</th>
<th>Number of subjects</th>
<th>Study design</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stehr-Green et al. [49]</td>
<td>Not available</td>
<td>Ecological</td>
<td>Sweden and Denmark</td>
</tr>
<tr>
<td>Madsen et al. [50]</td>
<td>956 (956)</td>
<td>Ecological</td>
<td>Denmark</td>
</tr>
<tr>
<td>Hvid et al. [51]</td>
<td>467 450 (440)</td>
<td>Retrospective cohort</td>
<td>Denmark</td>
</tr>
<tr>
<td>Verstraeten et al. [52]</td>
<td>140 887 (223)</td>
<td>Retrospective cohort</td>
<td>USA</td>
</tr>
<tr>
<td>Heron and Golding [53]</td>
<td>12 956</td>
<td>Prospective cohort</td>
<td>UK</td>
</tr>
<tr>
<td>Andrews et al. [54]</td>
<td>103 043 (106)</td>
<td>Retrospective cohort</td>
<td>UK</td>
</tr>
<tr>
<td>Fombonne et al. [44]</td>
<td>27 749 (61)</td>
<td>Ecological</td>
<td>Canada</td>
</tr>
</tbody>
</table>

Source: Based on Gerber and Offit [30].

¹ Number of autism cases in parentheses.
efficacy in numerous studies discussed in Section 4. In addition, most industrialised and a number of low and middle income countries, including South Africa, have independent national technical advisory bodies which use scientific evidence to guide national policymakers and programme managers on immunisation policies and programmes, called National Immunization Technical Advisory Groups (NITAGs) [62]. The South African NITAG is referred to as the National Advisory Group on Immunisation (NAGI), and is made up of eight leading academic experts in disciplines related to immunisation from universities throughout the country, a representative from the Medicines Regulatory Authority, as well as three ex-officio members from the EPI-SA, and one each from the United Nations Children's Fund and the WHO [63]. The scientific evidence on which the NITAGs have based their guidance and recommendations, has convinced governments and public health practitioners all over the world to recommend vaccination as the most cost-effective tool for the prevention and control of VPDs.

The public also needs to understand that many in the anti-vaccination lobby make a profit out of advocating alternatives to vaccination, or sell books promoting anti-vaccination, or attract parents with fears about vaccination to their websites in order to sell unrelated products. This is evidenced by many websites with anti-vaccination messages having links to online shopping, or promoting homeopathy or other alternative services [18,19,21,22,24,25].

• “Diseases have declined because of improved sanitation and nutrition, not because of vaccination”

It is true that improved housing, less crowded living conditions, improved education, reduced birth rates, better nutrition, water-borne sewerage, clean piped water, antibiotics and other medical treatments, have all greatly contributed to reduce the burden of infectious diseases. However, some anti-vaccination lobbyists claim that vaccination has played no part in the declining incidence [19,22,24], a claim that some South African anti-vaccination website owners have also adopted [21].

Contrary to these claims, ecological studies have shown that since the introduction of vaccines, the specific diseases they target have decreased dramatically in each country where they have been introduced. For example, in the USA, when the measles vaccine was introduced in 1963, there was an average of 503 282 cases per year; this was reduced to 44 cases in 2002. Also in the USA, when the rubella vaccine was introduced in 1969, rubella cases dropped from 57 686 (including 29 deaths), to only 18 cases in 2002 [28]. Again in the USA, when Hib vaccination was introduced in 1990, there were 20 000 Hib cases in that year, with only 1419 cases in 1993 [56]. Even long after the introduction of the older vaccines, as vaccination coverage has increased in different parts of the world, there has been a concomitant global reduction in these VPDs [64] (see Table 4).

Conversely, following vaccine scares when a government has withdrawn a vaccine from their EPI or vaccine coverage drops dramatically because of public fears, this has been followed by an outbreak of the disease [28,56]. For example, in response to vaccine scares when pertussis vaccination levels dropped, incidence increased dramatically, as was seen in the UK during 1974–1978, with 100 000 pertussis cases and 36 deaths, and in Japan from 1974 to 1979, with 13 000 pertussis cases and 41 deaths. In the 1990s low pertussis immunisation rates in the former Soviet Union resulted in an increase from 839 cases in 1989 to 50 000 cases and 1700 deaths in 1994 [56].

• “The risk of AEFIs is higher than the risk of the disease”

Vaccines have often been called “victims of their own success” [1,2,24,65]. Because they have been so successful at reducing the incidence of the diseases they target, the uncommon and rare AEFIs that they induce have become, in the view of the anti-vaccination lobby, more common and more feared than the diseases themselves [1,2,24,28,66]. Yet the diseases that vaccines prevent often have very serious complications that were very common in the pre-vaccination era, thus the risk of the disease far outweighs the risk of vaccination as can be seen in Table 5. Parents and HCWs seldom see the diseases that vaccines prevent, and thus many question the need for vaccines for what they perceive as rare and mild diseases. Most AEFIs are in fact very mild (tenderness, redness, and mild fever) and short-lived [56]. Very rarely is there a serious AEFI (1 per several thousands or millions, or so rare that one cannot calculate the risk [56,67]; see Table 5), but clearly for the families involved, serious AEFIs can be devastating events that cause them to seriously doubt the benefits of vaccination.

AEFIs are similarly viewed by some South African anti-vaccination internet bloggers and website owners as more common and more dangerous than the diseases they are meant to prevent often have very serious complications that were very common in the pre-vaccination era, thus the risk of the disease far outweighs the risk of vaccination as can be seen in Table 5. Parents and HCWs seldom see the diseases that vaccines prevent, and thus many question the need for vaccines for what they perceive as rare and mild diseases. Most AEFIs are in fact very mild (tenderness, redness, and mild fever) and short-lived [56]. Very rarely is there a serious AEFI (1 per several thousands or millions, or so rare that one cannot calculate the risk [56,67]; see Table 5), but clearly for the families involved, serious AEFIs can be devastating events that cause them to seriously doubt the benefits of vaccination.

The public also needs to understand that many in the anti-vaccination lobby make a profit out of advocating alternatives to vaccination, or sell books promoting anti-vaccination, or attract parents with fears about vaccination to their websites in order to sell unrelated products. This is evidenced by many websites with anti-vaccination messages having links to online shopping, or promoting homeopathy or other alternative services [18,19,21,22,24,25].

Table 4
The reduction of VPDs globally from 1980 to 2009.

<table>
<thead>
<tr>
<th>VPD</th>
<th>1980 reported global incidence and vaccination coverage</th>
<th>2009 reported global incidence and vaccination coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>97 511</td>
<td>857</td>
</tr>
<tr>
<td>Pertussis</td>
<td>1 982 355</td>
<td>106 207</td>
</tr>
<tr>
<td>Polio</td>
<td>52 795</td>
<td>1779</td>
</tr>
<tr>
<td>Measles</td>
<td>4 211 431</td>
<td>222 408</td>
</tr>
<tr>
<td>Source: WHO [64].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 5
Risk of disease versus risk of vaccination.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Risk of disease</th>
<th>Risk of vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Pneumonia: 1 in 20</td>
<td>Encephalitis or severe allergic reaction: 1 in 1 million</td>
</tr>
<tr>
<td></td>
<td>Encephalitis: 1 in 2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 in 5 in developing countries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 in 3000 in industrialised countries</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Death:</td>
<td>With DTaP:</td>
</tr>
<tr>
<td></td>
<td>1 in 20</td>
<td>Continuous crying followed by complete recovery: 1 in 1000</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Death:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25–70 in 100 generally</td>
<td>Acute encephalopathy: 0–10.5 in 1 million</td>
</tr>
<tr>
<td>Pertussis</td>
<td>10–20 in 100 with good intensive care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia: 1 in 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Encephalitis: 1 in 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 in 200</td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO [56] and CDC [67].
prevent [16,20,21], as previously reported [24,28,66]. The notion that childhood infectious diseases are mild or trivial has been found on the world-wide web for many years [22–24], and the practice of throwing parties for unvaccinated children when one of them has a VPD so that all can “naturally” be infected [2], is now being advocated by a homeopath interviewed by a South African newspaper published on the Internet [55].

There are also many (the vast majority) reported AEFIs that are totally unrelated to vaccination, which are recorded in registries and databases throughout the world as part of the routine procedure required for pre- and post-licensure evaluation. These AEFIs are purely coincidental, as they occur following vaccination, but are not caused by the vaccination (i.e. they are not adverse events caused by vaccination). However, it is not up to the individual HCW to assess if an AEFI is related or unrelated to vaccination, so all AEFIs are recorded and then reviewed by panels of experts who investigate whether a reported AEFI is actually caused by a vaccine. For example, if a child is vaccinated for measles while incubating an influenza infection and then presents with influenza symptoms shortly thereafter, this may be recorded as an AEFI despite it being merely coincidental and not caused by the measles vaccine. There are less clear-cut coincidental cases, as can be seen in the autism cases exploited by Wakefield and colleagues, and the anti-vaccination lobby. The first signs and symptoms of autism coincidentally appear at around the same age when children in the UK receive their MMR vaccines, thus it is not surprising that children who develop signs and symptoms of autism have coincidentally been vaccinated with MMR [14,28,30]. The parents of these children sometimes believe and vehemently support the misinformation propagated by the anti-vaccination lobby that the MMR was directly responsible for their child developing autism, as documented in their personal testimonies on the Internet [19,22,24].

5. Talking to parents who question vaccines

Addressing some of the difficult questions about the risks of vaccines that South African parents who have been exposed to anti-vaccination messages may ask of HCWs, has been covered in this paper. However, providing scientific evidence to questioning parents does not always result in parents being convinced to vaccinate their children [3]. Good communication and dialogue skills are needed [14,68]. Earning trust, creating awareness, deepening understanding, gaining agreement on solutions, and motivating action [69], are goals that HCWs need to strive for when communicating the risks and benefits of vaccination to parents.

Determinants of trust include the parents’ perception of the expertise of the HCW, as well as how open, honest, caring and concerned the HCW appears to be [3]. HCWs must first earn the parents’ trust before they can address their fears and suspicions [13,69]. First, the HCW should acknowledge the parents’ concerns [69], and then explain that there are safety measures in place to prevent AEFIs as far as possible, and that if they do occur, that they are extremely rare when compared to the risk of contracting the diseases that the vaccine(s) can prevent. Second, endorse fundamental expertise of the HCW, as well as how open, honest, caring and concerned the HCW appears to be [3]. HCWs must first earn the parents’ trust before they can address their fears and suspicions [13,69]. First, the HCW should acknowledge the parents’ concerns [69], and then explain that there are safety measures in place to prevent AEFIs as far as possible, and that if they do occur, that they are extremely rare when compared to the risk of contracting the diseases that the vaccine(s) can prevent. Second, endorse fundamental values [69]. For example, the health of South African children is EPI-SA’s most important priority, which is a fundamental value shared by all parents. Third, cast a positive identity [69]. For example, build self-confidence in parents by not ridiculing the source of misinformation that has led them to question vaccination, because they will feel defensive. Instead, empathise with parents who are genuinely worried about causing harm to their children, and give them a list of reputable books, journals and websites (such as SAVIC’s: www.savic.ac.za) that do publish credible articles on vaccination for lay people, and admit to using these sources and finding them helpful and interesting. Finally, the key is to ensure that the information is well understood, using terms that are not confusing or too technical [69].

6. Conclusion

Increasing numbers of South Africans are accessing misinformation about vaccinations on the Internet, which may have a negative impact on vaccination coverage in pockets of the country where Internet usage is widespread. Outbreaks that arise in these pockets because of vaccine refusal may spill over to other provinces where vaccination coverage is low for reasons other than vaccine refusal. The recent measles outbreak which started in Gauteng Province, the economic hub of the country with a high level of migrant labour, and then spread to all nine provinces, is a case in point. Thus it is crucial to monitor public questioning and concerns regarding vaccination in order to understand the concerns and respond appropriately in good time [3]. Research is needed to (a) characterise the South African anti-vaccination lobby; (b) investigate the psychological, socio-cultural, and political determinants that have led to loss of trust in vaccination by some South African parents; and (c) measure the impact of the anti-vaccination lobby on vaccination coverage. At the same time, steps need to be taken to ensure that HCWs involved in the EPI-SA fully understand this misinformation and are prepared to address some of the difficult questions and perceptions which they may be confronted with. HCWs should be allowed the time for dialogue with questioning parents, and be supported with information and skills to listen to, and engage with parents with empathy in a way that builds trust and allows for true understanding.

Conflict of interest statement

None declared.

References

Vaccination provides a powerful technological tool to improve the health of the world’s population. However, because of the nature of infectious disease transmission, no country can be entirely secure as long as reservoirs of infectious cases exist in any country; with increasing levels of travel and migration in many parts of the world including Southern Africa, continuous spread of vaccine-preventable and other infectious diseases is likely. A significant proportion of deaths of children under five years of age [3].

There is a high degree of acceptance of vaccination as a basic public good in South Africa and as an essential element of primary health care delivery. In addition to the usual childhood vaccines, South Africa has introduced four new generation vaccines:
Hepatitis B (1996), Haemophilus influenzae type b (1998) and Pneumococcal and Rotavirus vaccines (2008). In 2002 the Minister of Finance co-chaired a global conference of Ministers of Health and Finance on vaccination in Cape Town and was a patron of Global Alliance for Vaccines and Immunisation (GAVI). South Africa also contributes to the International Finance Facility for Immunisation and is an important global site for vaccine research on tuberculosis (TB) and HIV, illustrating the political will given to vaccines.

1.1. Financing vaccinations

Financing vaccines needs to be seen within the broader architecture of financing health care within specific countries. Health financing is often considered within a conceptual framework of raising revenue (sources of funds, financing mechanism, collecting agency), pooling (risk pools, resource allocation) and purchasing (benefit package, payment mechanisms). GAVI considers a good financing mechanism should be equitable, efficient (administratively not too expensive), effective (generates adequate, timely and reliable resources) and should promote accountability and self-sustainability [4].

Vaccines are generally considered a global public good. Given the nature of infectious diseases it is essential to ensure high enough levels of immunization coverage in order to achieve herd immunity, and reduce and possibly eliminate transmission. For this reason out of pocket payments that may prevent in particular the poor from seeking immunization services are generally a poor method of financing vaccines [5]. Where countries have multiple funding pools, a national regulatory framework for at least a set of minimum benefits (including access to immunization) is needed. There are many useful international publications on the pros and cons of different financing methods [4,6,7]. Besides the more usual methods of financing health services by governments and donors, various innovative methods have been put in place to assist in financing vaccinations on a global level especially to support low income countries or coordinate purchasing across regions. These include advance market commitments (AMC), volume guarantees, long-term purchase contracts, pooled procurement such as Pan African Health Organisation’s (PAHO) Revolving Fund, the International Finance Facility for Immunisation (IFFIm) and sector wide donor support (SWAp) [4,8].

2. Methodology

South African government budget documentation from 2008 to 2011 pertaining to new generation vaccines was reviewed, with a particular focus on criteria used to assess new generation vaccines for funding. Funding of vaccinations is presented in the context of recent health financing indicators from South Africa. Prices were determined initially in South African Rand and are presented in $US for purposes of international comparison based on an average exchange rate of R8.25 in 2008.$1. Trends in health expenditure were analysed from publications and databases of the National Treasury (Department of Finance) in South Africa, such as the annual Budget Review [9] and the two yearly Inter-governmental Fiscal review series [10]. Comparisons of global spending by government on health services were derived from the World Health Organisation [11]. Fiscal space was assessed through national indicators including trends in domestic revenue, government expenditure, fiscal deficit, and debt as proportion of gross domestic product (GDP), and interest expenditure as a proportion of total expenditure.

3. Results

3.1. Financing vaccination in South Africa

South Africa is a middle income country and so does not qualify for GAVI support. Despite relatively slow economic growth, its fiscal position has generally been stable with low levels of public debt (33.8% of GDP in 2011/12) and relatively small budget deficits (although these have increased during the recent global recession). Its total level of government revenue, mainly from taxation, amounted to 28.4% of GDP in 2011/12 (as compared for example to 40% in a developed country such as the UK) [9]. These factors have contributed to some fiscal space to increase spending on vaccination, in the context of a high burden of disease, increasing prioritization of health by government and a relatively average level of health financing compared to other middle income countries [11].

In South Africa, approximately 83% of the population of 50.5 million is uninsured and relies primarily on public services; 17% of the population is insured by mainly private health insurance called medical schemes [12]. South Africa is in the process of developing a National Health Insurance (NHI) system, however this is still in the process of policy and legislative development [13]. Total expenditure on health services amounts to 8.5% of GDP in 2011/12, of which 4.2% is from public sources, 4.1% from private sources and 0.2% from donors [10]. Public sector health services (and thus vaccines) in South Africa are financed predominantly in the public sector through general tax revenue. The sources of funds for general tax revenue are mainly personal income tax (36.7%), corporate income tax (19.8%) and value added tax (24.8%). Spending on public sector health services has increased from 3.4% of GDP in 1995/96 to 4.2% in 2011/12 or from 3% to 3.9% using a narrower definition (Department of Health only, excluding other government departments and entities, spending on healthcare).

The vaccination programme is financed virtually entirely through domestic resources. All vaccines provided through the public sector are free at the point of use (i.e. no user charges). The budget for vaccines (medicines component only) is approximately $131 million (R1.08 billion) in 2011/12. Costs of personnel and other components of visit costs are estimated at approximately $57 million per annum (R469m). The introduction of new generation vaccines led to a fivefold increase in expenditure on vaccines (fourfold in real terms) (Table 1). Despite constituting approximately 13% of public sector medicine expenditure, total spending on vaccines amounts to just under 1% of expenditure on public health services in South Africa. This, makes even new generation vaccines

| Table 1 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Budget for vaccines and as a proportion of total spending on public sector health services (nominal Rand million). |
| Health spending | 43,040 | 49,806 | 56,719 | 65,930 | 79,015 | 93,020 | 102,890 | 115,099 |
| Spending on Medicines, total | 3,129 | 3,705 | 4,538 | 4,905 | 5,494 | 6,403 | 8,042 | 8,267 |
| Vaccines | 188 | 207 | 209 | 219 | 320 | 464 | 802 | 1,080 |
| Vaccines spending as a % of Medicine spending, total | 6.0% | 5.3% | 4.6% | 4.5% | 5.8% | 10.1% | 10.7% | 13.1% |
| Health spending, total | 0.4% | 0.4% | 0.4% | 0.3% | 0.4% | 0.7% | 0.8% | 0.9% |

relatively affordable. Latin American countries that have been rapid adopters of new vaccines generally spend around 1% of their health budgets for vaccine purchases. A recent analysis of the 15 countries expected to graduate from GAVI support by 2015 and become financially self-sufficient thereafter also suggests that most of them will be able to pay for all vaccines using less than 1% of estimated future public spending for health [14].

In the private sector, although medical schemes have regulatory imposed prescribed minimum benefits, these are not always perfectly aligned with the public sector vaccination programme. This means that users in the private sector sometimes pay out-of-pocket for vaccines administered by private providers, even though they have the option of receiving them free of charge at public facilities.

Table 2 shows health spending in the context of total government expenditure on the main budget in nominal terms (i.e. not adjusted for inflation). Each year as the GDP grows this leads to revenue increases and additional funds become available for allocation. These amounts increase further if tax policy makes provision for revenue as a proportion of GDP to rise, as it did from 2004/05 to 2008/09. As it happened the rollout of some of the new generation vaccines in the 2009/10 year was followed shortly by the onset of the global economic recession (see reduced revenue: GDP ratio in 2009/10), but government maintained spending levels of social services through the recession by temporarily increasing the deficit (see difference between expenditure and revenue). Health expenditure has increased by on average R10 billion ($1.2 billion) per annum in nominal or current terms (R5 billion or $606 million in real terms) over the period from 2004/05 to 2011/12 and in this context the introduction of new generation vaccines has been relatively affordable.

Comparing the level of government spending for health services across middle income countries (Table 3), South Africa’s level of spending (despite the WHO numbers varying slightly from what was presented above) is fairly comparable with that of other middle income countries with similar levels of economic development as measured by percentage of GDP (3.9% for South Africa in Table 2 vs. 3.5% upper middle income average in Table 3). However South Africa’s health outcome indicators are considerably poorer, mainly driven by HIV. It has been estimated that the cost of HIV for public health services alone is approximately 0.7% of GDP in 2011/12 and this cost continues to rise [15,16]. Given the higher burden of disease in South Africa it has been suggested that spending should be above the average for middle income countries.

### 3.2. Economic evaluation of new vaccines

As the financial implications of introducing new vaccinations are fairly substantial they usually require additional resources. In the South African context, given that the vaccination schedule is set through national policy and thus raises similar financial implications for all levels of government, the introduction of new vaccines is typically addressed in the annual round of budget negotiations.

The tabling and consideration of new budget bids by government in South Africa requires inclusion of a range of sufficient evidence to enable the evaluation of the bid. Criteria that have proved useful repeatedly in the South African context include:

- **Burden of disease:** data reported by the National Department of Health.
- **Effectiveness of the vaccine:** published studies in reputable international journals, if possible meta-analysis or Cochrane reviews.
- **Cost-effectiveness of the vaccine:** while international studies provide useful information, local studies are usually required, given very different cost structures across countries.
- **Total cost and affordability:** depends on fiscal space, prioritization, success in price negotiations and contracting.
- **Feasibility of implementation and availability of a credible implementation plan:** If there are doubts about feasibility, pilot studies may be useful.
- **International guidelines and advice of the South African National Advisory Group on Immunisation (NAGI) and other local and international experts.**
- **Political process:** Besides the technical aspects, the budget process also involves communication between the Ministers of Health and Finance and approval by a wider committee of Ministers, the national Cabinet and Parliament.

#### 3.3. Protecting funding at a sub-national level

South Africa consists of nine provinces which are responsible for operational aspects of health service delivery. Provinces have substantial powers over financial allocations [17,18] and although they have historically had relatively limited discretion in introducing new vaccines there is risk that each province may fund national programmes in a different manner. To address, this several mechanisms were put in place to ensure greater consistency in the approach to adoption and uptake of new vaccines. Changes to the vaccination schedule were thoroughly discussed at a number of inter-governmental forums which coordinate activities across the various levels of government. New vaccination schedules were released as national policy with appropriate guidelines and extensive training was initiated. The new policy was identified as a budget priority and provinces were required to report back to the national level on their proposed budgets for priority areas prior to finalization of the budget process. Conditional grants are a potential mechanism to earmark and protect funding allocated at the

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**Table 2**  
Health spending in context of overall fiscus.  

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP</td>
<td>1,431</td>
<td>1,580</td>
<td>1,807</td>
<td>2,082</td>
<td>2,320</td>
<td>2,443</td>
<td>2,667</td>
<td>2,915</td>
</tr>
<tr>
<td>Revenue: GDP ratio</td>
<td>24.3%</td>
<td>26.1%</td>
<td>26.6%</td>
<td>26.9%</td>
<td>26.2%</td>
<td>23.9%</td>
<td>24.8%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Total government revenue</td>
<td>348</td>
<td>412</td>
<td>481</td>
<td>560</td>
<td>609</td>
<td>585</td>
<td>660</td>
<td>730</td>
</tr>
<tr>
<td>Total government expenditure</td>
<td>369</td>
<td>417</td>
<td>470</td>
<td>541</td>
<td>636</td>
<td>743</td>
<td>810</td>
<td>885</td>
</tr>
<tr>
<td>Health spending as a proportion of total government expenditure in main budget</td>
<td>11.7%</td>
<td>12.0%</td>
<td>12.1%</td>
<td>12.2%</td>
<td>12.4%</td>
<td>12.5%</td>
<td>12.7%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Health spending in public sector (narrow)</td>
<td>43</td>
<td>50</td>
<td>57</td>
<td>66</td>
<td>79</td>
<td>93</td>
<td>103</td>
<td>115</td>
</tr>
<tr>
<td>Health spending in public sector (narrow) as % of GDP</td>
<td>3.0%</td>
<td>3.2%</td>
<td>3.1%</td>
<td>3.2%</td>
<td>3.4%</td>
<td>3.8%</td>
<td>3.9%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Source: National Treasury databases and publication series [9,10].

* Numbers are expressed in nominal terms (i.e. not adjusted for inflation) in SA Rand.
* Narrow refers to national and provincial Departments of Health only and excludes health related spending by other departments and entities.

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*Table 3*  
Health and Finance and approval by a wider committee of Ministers, the national Cabinet and Parliament.
Unlike diphtheria, whooping cough and tetanus which have been virtually eliminated in South Africa, pneumonia is amongst the top four causes of mortality of South African children under five years of age, pneumococcus being the most common cause. Local data provided by the National Advisory Group on Immunisation estimated there are 100,000 cases of pneumonia annually with high fatality rates among the severe cases, which number 14,500–16,000 per annum. South Africa has a Cochrane centre. The Cochrane review [19] meta-analysis and the results of several trials were considered. As it happened one of the early landmark trials was done in South Africa, showing the vaccine’s effectiveness to be 65% in HIV-infected children and 83% in HIV-uninfected children [20].

Cost-effectiveness: According to WHO-CHOICE guidelines for low and middle income countries, interventions which cost less than GDP per capita can be regarded as highly cost-effective and between one to three times GDP per capita as cost-effective [21]. Local estimates of cost effectiveness calculated by the National Treasury and National Advisory Group on Immunisation ranged from R4,312 to R11,109 per DALY averted ($523–$1,347). This is less than national GDP per capita (R51,500) and was considered highly cost-effective.

Table 3
Comparing government spending on health across selected middle income countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>Gov health expenditure as % of GDP</th>
<th>GDP per capita (current US$)</th>
<th>Per capita gov health expenditure (PPP$ int $)</th>
<th>Total health expenditure as % of GDP</th>
<th>Gov health expenditure as % of total health expenditure</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chile</td>
<td>3.4 3.6 9877</td>
<td>320 507</td>
<td>207 6.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 6.2</td>
</tr>
<tr>
<td>Mexico</td>
<td>2.4 2.7 9741</td>
<td>236 372</td>
<td>207 5.9</td>
<td>320 507</td>
<td>320 507</td>
<td>207 5.9</td>
</tr>
<tr>
<td>Russia</td>
<td>3.2 3.5 9146</td>
<td>247 512</td>
<td>207 5.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 5.4</td>
</tr>
<tr>
<td>Turkey</td>
<td>3.1 3.5 8865</td>
<td>272 467</td>
<td>207 4.9</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.9</td>
</tr>
<tr>
<td>Venezuela</td>
<td>2.4 2.7 8252</td>
<td>199 324</td>
<td>207 5.7</td>
<td>320 507</td>
<td>320 507</td>
<td>207 5.7</td>
</tr>
<tr>
<td>Uruguay</td>
<td>6.1 5.9 7206</td>
<td>500 678</td>
<td>207 11.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 11.2</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.9 3.5 7185</td>
<td>202 348</td>
<td>207 7.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 7.2</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1.7 2.0 7028</td>
<td>159 268</td>
<td>207 3.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 3.2</td>
</tr>
<tr>
<td>Argentina</td>
<td>5.0 5.1 6604</td>
<td>452 671</td>
<td>207 9.0</td>
<td>320 507</td>
<td>320 507</td>
<td>207 9.0</td>
</tr>
<tr>
<td>Botswana</td>
<td>2.7 4.3 6545</td>
<td>218 568</td>
<td>207 4.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.4</td>
</tr>
<tr>
<td>South Africa</td>
<td>3.4 3.6 5933</td>
<td>223 340</td>
<td>207 8.5</td>
<td>320 507</td>
<td>320 507</td>
<td>207 8.5</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>5.0 5.9 5891</td>
<td>360 656</td>
<td>207 6.5</td>
<td>320 507</td>
<td>320 507</td>
<td>207 6.5</td>
</tr>
<tr>
<td>Namibia</td>
<td>4.2 3.2 4216</td>
<td>174 196</td>
<td>207 6.1</td>
<td>320 507</td>
<td>320 507</td>
<td>207 6.1</td>
</tr>
<tr>
<td>Peru</td>
<td>2.8 2.5 3771</td>
<td>134 191</td>
<td>207 4.7</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.7</td>
</tr>
<tr>
<td>Thailand</td>
<td>1.9 2.7 3689</td>
<td>89 209</td>
<td>207 3.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 3.4</td>
</tr>
<tr>
<td>China</td>
<td>1.8 1.9 2651</td>
<td>42 104</td>
<td>207 4.6</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.6</td>
</tr>
<tr>
<td>Morocco</td>
<td>2.0 2.3 2373</td>
<td>32 68</td>
<td>207 4.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.2</td>
</tr>
<tr>
<td>India</td>
<td>1.1 1.1 1096</td>
<td>16 29</td>
<td>207 4.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.4</td>
</tr>
<tr>
<td>Vietnam</td>
<td>1.6 2.8 804</td>
<td>23 72</td>
<td>207 5.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 5.4</td>
</tr>
<tr>
<td>Low income</td>
<td>1.8 2.2</td>
<td>14 28</td>
<td>207 4.7</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.7</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>1.6 1.8</td>
<td>35 76</td>
<td>207 4.4</td>
<td>320 507</td>
<td>320 507</td>
<td>207 4.4</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>3.2 3.5</td>
<td>243 419</td>
<td>207 6.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 6.2</td>
</tr>
<tr>
<td>High income</td>
<td>6.1 6.9</td>
<td>1631 2492</td>
<td>207 10.2</td>
<td>320 507</td>
<td>320 507</td>
<td>207 10.2</td>
</tr>
</tbody>
</table>


PPP: Purchasing Power Parity.

3.4. Case study: pneumococcal vaccine

Pneumococcal conjugate vaccine (PCV) was first licensed for use and introduced in the private sector in South Africa in 2005 with the public sector introducing it from the latter half of 2008. Some of the key criteria used in the evaluation were:

Burden of disease: Unlike diphtheria, whooping cough and tetanus which have been virtually eliminated in South Africa, pneumonia is amongst the top four causes of mortality of South African children under five years of age, pneumococcus being the most common cause. Local data provided by the National Advisory Group on Immunisation estimated there are 100,000 cases of pneumococcal pneumonia annually with high fatality rates among the severe cases, which number 14,500–16,000 per annum. South Africa has a high rate of child mortality (57/1000) which motivated strongly for intervention.

Effectiveness: Strong evidence was available on effectiveness of pneumococcal conjugate vaccine. South Africa has a Cochrane centre. The Cochrane review [19] meta-analysis and the results of several trials were considered. As it happened one of the early landmark trials was done in South Africa, showing the vaccine’s effectiveness to be 65% in HIV-infected children and 83% in HIV-uninfected children [20].

Cost-effectiveness: According to WHO-CHOICE guidelines for low and middle income countries, interventions which cost less than GDP per capita can be regarded as highly cost-effective and between one to three times GDP per capita as cost-effective [21]. Local estimates of cost effectiveness calculated by the National Treasury and National Advisory Group on Immunisation ranged from R4,312 to R11,109 per DALY averted ($523–$1,347). This is less than national GDP per capita (R51,500) and was considered highly cost-effective.

Total cost and affordability: In South Africa approximately 1.066 million children are born annually [22]. For the purpose of assessing feasibility and affordability prior to procurement, the unit price was estimated at R600 per course ($73, or $24.30 per dose) based on early discussions with suppliers. The total cost estimated at 85% coverage was R542 million per annum ($65.7 million). This was considered too large to be addressed within a single budget, but sufficient fiscal space existed for it to be reached by year two or three, if the intervention could be progressively rolled out. With the benefit of hindsight, these initial unit costs can be considered relatively high, and subsequently turned out to be more expensive than PAHO and GAVI prices [23,24]. However early adoption of the vaccine was deemed imperative, and it was thought likely that cheaper prices would be obtained over time as global and domestic volumes increased, generic and innovator competition entered the market, and improved intelligence on global pricing patterns was obtained. Costs were partially offset by a frontloaded in-kind donation of additional doses and support for cold chain capacity, training of health workers, disease monitoring and social mobilisation and communication, which improved the short-term affordability. While bundling was not a necessity, it was the outcome of negotiations with the single supplier, who made offers of additional support which enabled the early rollout of the vaccine. Various complexities regarding pricing and affordability are considered further in the discussion section below.

Feasibility: Pneumococcal vaccine could easily be incorporated into the routine child immunization schedule, and could be given simultaneously with a new pentavalent combined vaccine. A seven-valent pneumococcal strain was introduced as a short-term decision, as it was the only product licensed and registered at the time (South Africa has since introduced the 13-valent vaccine in 2011). The National Health Laboratory Service has a pneumococcal surveillance programme that monitors incidence and mortality rates. Additional provision will be made for cold chain requirements and extensive training will be implemented on the revised...
schedules. Countries such as the UK and Australia had recently introduced the vaccine successfully.

**International guidelines:** In 2007 the World Health Organisation vaccination recommendations were widened to include pneumococcus, recommending prioritisation in countries with a high level of infant mortality, a high number of annual deaths or in countries with a high prevalence of HIV. In 2008 their use and funding support for low income countries was recommended by GAVI.

**Expert advice:** The South African National Advisory Group on Immunisation (NAGI) strongly recommended introduction. This view was backed by several leading paediatricians, infectious disease specialists and the South African Medical Research Council.

**Political process:** Budget bids are tabled by the Minister of Health to the Minister of Finance. The bid for vaccine introduction followed extensive technical advice from NAGI and detailed discussions with provinces. Budget recommendations were approved by national Cabinet and Parliament noting the priority of maternal and child health given poor child survival indicators.

**Conclusion:** The overall assessment process was systematic and the findings were extremely positive. The only borderline concern was affordability, however the earliest possible adoption of the vaccine was deemed imperative, and prices were expected to fall reasonably quickly. On the basis of this positive evaluation, $131 million (R1.08 billion) was allocated over three years for new vaccines in Budget 2009, with annual allocations rising over three years in line with affordability. The vaccine was introduced mid-year in 2008 in a number of pilot sites and national rollout commenced in 2009. Full national rollout could only be afforded by the third year. Negotiated arrangements with pharmaceutical companies to front-load higher volumes allowed for earlier roll-out. In 2011, based on greater competition and transparency about international prices, South Africa has been able to re-negotiate substantially lower prices (see Section 4).

3.5. Case study: rotavirus vaccine

**Burden of disease:** South Africa has a high child mortality rate (57/1000). Diarrhoea is the third major cause of mortality in infants (10,786 deaths in 2000) and is especially high among poor children. Rotavirus causes 25–50% of child diarrhoea, 3,591–5,383 child deaths and 25–58% (30,000) of hospitalisations due to diarrhoea (personal communication National Health Laboratory Service and NAGI). The majority of rotavirus infections occur in children under one [25,26].

**Effectiveness:** At the time the decision was taken, substantial evidence was available that rotavirus vaccines are effective in preventing rotavirus infections, particularly serious infections with a 2004 Cochrane review of 64 trials reported effectiveness in preventing 43–90% of severe cases [27,28]. Rotavirus vaccine immunogenicity and safety trials had demonstrated effectiveness and safety in the countries where these trials were conducted, including in Europe, and in North and South America [29,30]. Interim results of a landmark South African and Malawian study [31] became available in 2008 and once published [32] helped to pave the way for revisions in global guidelines for rotavirus [33].

**Cost-effectiveness and cost–benefit:** Several published studies were available showing cost-effectiveness in Asia, Vietnam, Mexico and the USA [34–37]. A local cost–benefit analysis provided by the National Advisory Group on Immunisations suggested benefits of reduced hospitalization alone would cover much of the costs of introducing the new vaccine. Unit costs were expected to decrease over time noting international comparisons [24,38].

**Total cost and affordability:** Total cost for 1.06 million children was estimated at $22 million per annum (85% coverage, $24 per course). This was considered affordable in the South African context (0.17% of total health expenditure).

**Feasibility:** SA has a well-established, high coverage vaccination programme and the new vaccine could be added with limited difficulty to the routine child immunisation schedule. Rotavirus is an oral vaccine, and the need for training of health care workers, upgrading of cold chain capacity and other administration issues were considered feasible in the South African context, despite short term health systems weaknesses. Countries in Latin America had recently introduced the vaccine successfully.

**International guidelines:** In 2008, GAVI endorsed the use of the rotavirus vaccine and was on the point of subsidising its use in low income countries. WHO had prequalified products in 2007 and UNICEF approved its use. From 2007 WHO recommended use of the vaccine in countries where infrastructure and financing was available and where efficacy data showed a significant public health impact [39] and from 2009 for all countries [33].

**Expert advice:** NAGI and local paediatric and infectious disease experts supported its introduction.

**Political aspects:** Support was provided from the National Department of Health following a large outbreak of diarrhoea deaths in the Ukuhlamba district of Eastern Cape in a context of high child mortality rates in South Africa.

**Conclusion:** The decision to introduce the vaccination was driven by the high burden of rotavirus disease, evidence that the vaccine could substantially reduce incidence of severe cases and support from local experts (NAGI) and global organisations (GAVI, WHO). Immunisation for rotavirus appeared to have a positive cost–benefit ratio given high incidence of childhood diarrhoea and related morbidity and mortality in South Africa. The vaccine was funded for implementation from late 2008. South Africa was – the first country in Africa to introduce rotavirus vaccine. Since its adoption, the WHO Strategic Advisory Group of Experts have reviewed the data from efficacy studies conducted in Africa and has recommended the universal inclusion of rotavirus vaccines in national immunization programs.

4. Discussion

4.1. Decision making in South Africa

South Africa provides a useful country case study for financing vaccinations because it has been a fairly early adopter of new vaccines financed virtually exclusively from domestic resources. The analysis shows that despite the higher costs of new generation vaccines, they have been considered affordable given that they constitute a relatively small portion of the health budget (0.9%) while contributing to important outcomes of decreasing child morbidity and mortality. Standard health economic criteria of burden of disease, effectiveness, cost-effectiveness and affordability provided a fairly straight forward and robust way for the country to evaluate the new interventions. On this basis, considerable additional allocations were made leading to a fivefold increase in the vaccines budget.

The technical assessments required for effectiveness, cost-effectiveness and affordability are not unduly complex and these processes have been facilitated by the presence of a strong national vaccine advisory committee and some strong domestic institutions such as the National Institute of Communicable Diseases in the National Health Laboratory Service and the Medical Research Council. These decisions were enabled by the presence of fiscal space, sound macro-economic policy, debt and fiscal management and in the context of a well functioning national revenue service. The decisions were supported by good data from international trials including a meta-analysis (including support from the local Cochrane collaborating centre), clear global recommendations from WHO and GAVI along with expert local advice. The decision was also supported by political prioritization of health and the
need to address relatively poor child survival rates. When all of the evidence and other factors were combined, the government came to the conclusion that the new vaccines represented good value for money and their adoption should be an important component of the national strategies for improving child health.

Where affordability was borderline the intervention was rolled-out over a period of two to three years, to take advantage of progressively increasing availability of public funds and the fact that it can take several years to scale up a new vaccine intervention (even when the new technology can be relatively easily integrated within existing health services).

4.2. Pricing and affordability

Pricing is integrally linked to questions of affordability and universal roll-out of new generation vaccines. In South Africa, purchasing of vaccines is undertaken through a central transversal tender, conducted by a public private partnership, specifically established for the supply and local manufacturing of vaccines. With the benefit of hindsight, lower prices could possibly have been achieved in the initial tender. However given the urgency of introduction of the new vaccines it was considered imperative to embark rapidly on the rollout. Various complexities need to be considered in relation to pricing. It is now generally accepted that vaccine prices should be tiered by country income group, acknowledging the need for innovation and appropriate incentive arrangements to encourage new vaccine development such as for malaria, TB and HIV [40]. Costs for pneumococcal vaccine appear to vary from $7 per dose in GAVI eligible countries (half of which is subsidised [41]), $10–15 a dose for lower-middle income countries, and around $20, (with an upper limit of $30 used in the sensitivity analysis) in upper middle income countries [42]. PAHO appears to have secured a price of $15 per dose [38].

When South Africa entered into initial purchasing arrangements in mid-2008 this preceded the PAHO and GAVI pooled procurement processes. At the time, there was a single innovator supplier. Prior to the tender, the prevailing price in the private sector in the country was more than twice as expensive (personal communication National Health Laboratory Service and NAGI). The country had experienced with the introduction of new antiretroviral medication a pattern of initially high prices as a result of a single innovator company and low volumes, followed by a series of rapid price decreases as greater competition and higher volumes entered the market. At the time of writing it appears likely that pricing reductions of the order of 30–40% will be obtained in the second tender for pneumococcal vaccine to be awarded in the 2011/12 financial year.

Although South Africa has been able to afford the new generation vaccines, it initially paid more than other similar income countries, for example in Latin America [24] and substantially more than low income countries [23]. While the need for tiered pricing for vaccination is understood [4] (some of this may relate to a willingness to pay a premium for innovation to encourage new vaccine development) part of this relates to limited availability of information on global pricing patterns and benchmarks. Efforts to improve intelligence on global price benchmarks and prices being offered to other countries could also help to speed up the pace of price decline and enhance affordability. Substantial use of international price benchmarking and vastly improved availability of information on medications for HIV and AIDS from Médecins sans Frontières (MSF) and the Clinton Health Access Initiative (CHAI) amongst others [43] played an important role in achieving lower prices in a recent South African national tender for AIDS medicines. Similar global benchmarking information on vaccine pricing might allow more middle income countries to negotiate affordable prices and thus speed up universal rollout of new generation vaccines.

The global community may be able to assist countries by facilitating the creation of more open and transparent systems for tracking vaccine prices and for refining the basis for fair price tiering [40].

Other strategies include pooled procurement, technology transfer arrangements, and improving the regulatory environment. Regional or global purchasing arrangements such as through PAHO or GAVI [40] have helped bring down prices and improve access, and might be useful for a wider set of countries. Consideration should be given to introducing such arrangements for the Southern African Development Community (SADC) region or to building stronger cooperative agreements with GAVI, UNICEF and PAHO. Even if South Africa does not formally purchase using these mechanisms it might benefit through closer relationships to receive greater intelligence on pricing with these structures. The government did not explore technology transfer arrangements, as those designed in Brazil BioManguinos, an area that is currently being explored in the new tenders. A recent practice note by the South African Treasury makes publication of tender awards mandatory [44]. More rapid and efficient regulatory registration processes (e.g. for WHO pre-qualified products) to bring products to market earlier and introduce competition are also likely to assist in price reduction.

4.3. Programmatic issues and impact of the rollout

A 2011 WHO/UNICEF/NDOH study [45] evaluated the introduction of the new vaccines, noting that the training for the new vaccines was properly organized, and well cascaded to facility level in all provinces. However it cited some serious challenges including poor data collection, vaccination stock shortages, and shortage of cold chain capacity. There has also been poor collaboration between the public sector support for new generation vaccines and the regulatory aspects of prescribed minimum benefits for private medical schemes, with no accompanying revision of the latter. This led to an inconsistency in the public and private financing environments suggesting a need to coordinate basic benefits across different financing streams and for the regulatory approach to be aligned with policy changes.

These logistical and operational weaknesses suggest greater attention should have been given to planning and to various additional costs of complementary inputs required for rollout. Some form of earmarking of the funds allocated, such as through a new conditional grant, might have made for smoother rollout.

Despite these challenges, the implementation and rollout of the two vaccines was achieved rapidly and has seen some success. In just one financial year from 2009/10 to 2010/11, coverage increased from 22.8% to 72.8% for pneumococcal vaccine, and 34.6% to 72.8% for rotavirus vaccine [46,47]. Initial information on child health outcomes is also promising. Early indications from the National Health Laboratory Service shows the reduction of invasive pneumococcal disease in children under two by 61% [48] and a local case control study on the effectiveness of PCV7 in South Africa, suggests a reduction of between 27.3% and 58.9% of all presumed bacterial pneumonia (PBP) [49]. Mortality data from Statistics South Africa suggest that that total deaths for children under five reduced by 17.3% between 2008 and 2009 (StatsSA, mortality and causes of death: findings from death notification 2011), while data from the South African Medical Research Council suggests a 16% reduction of child deaths from 2008 to 2010 (personal communication Medical Research Council). However these improvements in outcomes are not necessarily attributable to the new vaccines and coincide also with improvements in HIV prevention of mother-to-child transmission and treatment programmes.
4.4. Financing vaccines

The country case studies suggest that it is relatively easy to assess the potential of countries to domestically fund their own vaccination programmes, using a simple set of indicators such as national GDP, a minimum level of public funding for health as a proportion of GDP (e.g. 2%), and affordability based on the share of vaccine costs in total government health expenditures (e.g. 1–1.5%). There is a set of low income countries that (even if they were to increase health spending as a proportion of GDP) do not have a sufficient GDP base to generate sufficient revenue for public health services. These countries are likely to remain partially dependent on global financing support. Approximately 72 countries were candidates for GAVI support at a per capita income of <US$1 000. Given the increase of global GDP/capita amongst low income countries, the eligibility cut off increased to $US1 500 per capita in January 2011 and 16 countries are anticipated to graduate from GAVI assistance by 2015 [14]. The need for such bilateral, multilateral and donor support has been reported by a number of global studies which usefully cost basic packages of health services and highlight the importance of health in economic development [50]. In contrast a middle income country such as South Africa should be able to fully fund its vaccination programmes, although donors may play a transitional role in introducing new initiatives since domestic budget cycles and scaling up of funding levels can take time.

The introduction of Human Papilloma Virus (HPV) vaccine may be the next vaccine candidate to be evaluated for introduction in South Africa. Preliminary analysis suggests that although the vaccine is relatively expensive, this has not been the primary barrier to its implementation, but rather the relatively poor state of school health services and difficulty of reaching pre-adolescents most at risk. Attention is being given to strengthening these services, while cost and cost-effectiveness are further analyzed.

5. Conclusion

South Africa provides a useful case study of a middle income country that has been an early adopter of new generation vaccines. In a context of relatively high child mortality, vaccines are considered a priority intervention and a public good. Introduction of new vaccines is predominantly tax funded from the central level (although some difficulties may arise in maintaining prioritization of funds at provincial level). Evaluation of new vaccines for funding follows fairly standardized economic evaluation techniques of effectiveness, cost-effectiveness and affordability. Although new generation vaccines have led to a fivefold increase in spending on vaccine products, spending is still less than 1% of the public health budget and the introduction of new generation vaccines has been considered cost-effective.

The successful introduction of new vaccines in middle income countries is likely to be facilitated by:

- Improved understanding of effectiveness, cost-effectiveness and cost–benefit ratios for new generation vaccines.
- Better access to information on global pricing and benchmarks.
- Further development of global and regional partnerships such as for purchasing and information sharing.
- Improved regulatory processes to bring new products and competition earlier to the market.
- Appropriate incentive design to reward new vaccine development and innovation.

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