

## NTAGI Subcommittee Recommendations on *Haemophilus influenzae* Type b (Hib) Vaccine Introduction in India

SUBCOMMITTEE ON INTRODUCTION OF HIB VACCINE IN UNIVERSAL IMMUNIZATION PROGRAM,  
NATIONAL TECHNICAL ADVISORY GROUP ON IMMUNIZATION, INDIA

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**Background:** WHO estimates that *Haemophilus influenzae* type b (Hib) caused over 8 million cases of serious disease and 376,000 deaths globally in the year 2000. The introduction of Hib vaccines has essentially eliminated Hib disease in countries where they are routinely used. Now, almost all Hib disease cases and deaths occur in countries where Hib vaccines is not incorporated in the routine immunization program.

**Process:** The Hib and Pneumococcal subcommittee of National Technical Advisory Group on Immunization (NTAGI) in India met in April 2008. This paper focuses on the discussions regarding Hib vaccine introduction; the pneumococcal vaccine discussion is being published separately. The subcommittee reviewed the available published and unpublished literature as well as consulted prominent Hib experts to make an informed decision regarding the introduction of Hib vaccine into the routine Universal Immunization Program (UIP) in India.

**Objectives:** The meeting was conducted with the objectives of reviewing the existing Indian, regional and global data on Hib disease (meningitis and pneumonia), the data on safety and immunogenicity of Hib vaccines

manufactured in India, as well as the programmatic and operational requirements for the introduction of Hib vaccine in India, with the goal of making a recommendation on the introduction of Hib vaccine into the UIP.

**Recommendations:** The committee noted that Hib diseases burden is sufficiently high in India to warrant prevention by vaccination. Hib vaccines have been demonstrated to be safe, both globally and in India, and extremely efficacious in all settings where they have been used. Hib vaccine fits into the UIP immunization schedule. Several Indian manufacturers are currently producing Hib vaccines, and a detailed analysis showed that supplier capacity would be sufficient to meet the present and future demand for India if given sufficient lead time to increase production. Recognizing that it is the poorest children that are most at risk, the Indian Academy of Pediatrics has already recommended this vaccine for routine use in India. This subcommittee strongly recommended that Hib vaccine should immediately be introduced in India's UIP.

**Key words:** *H. influenzae*, Hib vaccine, India, Recommendations.

The National Technical Advisory Group on Immunization (NTAGI) appointed a subcommittee to provide recommendations regarding the introduction of *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines in the Universal Immunisation Program (UIP). The subcommittee met on April 16-17, 2008 at the Indian Council of Medical Research, New Delhi. The purpose of this document is to present the process and outcome (consensus recommendations) regarding the introduction of Hib vaccine. The recommendations

of the subcommittee have been submitted to NTAGI. A document with the summary and recommendations on pneumococcal vaccine will be submitted separately for publication. The list of participants who attended the meeting is in *Appendix 1*.

### INTRODUCTION

India's Multi Year Plan (2005-10) for immunization(1) addresses the need for "accelerated introduction of new and underutilized vaccines against diseases with significant morbidity and

mortality in India". Four criteria are outlined for the introduction of new vaccines into the UIP: (i) the disease burden should be judged to be sufficient to warrant the introduction; (ii) the vaccine should be safe and effective; (iii) the cost of the vaccine should be reasonable and suitable for absorption into budget provision even if the introduction is funded, and; (iv) financial sustainability should be built into the plan of new vaccine introduction. Against this background, the subcommittee set the following objectives for the discussion regarding Hib vaccines:

- Review the available data on Indian, regional and global burden of Hib disease to assess the need for Hib vaccine introduction in UIP. The list of documents reviewed is given in *Appendix 2*.
- If consensus is to recommend its introduction, to define appropriate options including operational strategies for introduction of Hib vaccine in UIP.
- To identify needs for additional research including evaluation of the impact of Hib vaccine introduction.

## EPIDEMIOLOGY OF HIB DISEASE

### *Global Burden of Disease*

The WHO estimates that globally Hib caused over 8 million cases of serious disease and 376,000 deaths in the year 2000. (WHO; In press). Pneumonia and meningitis comprise the majority of the severe diseases caused by Hib in developing countries. Meningitis is the most severe form of Hib disease, with case fatality rates ranging from 20-25% and rates of severe neurologic sequelae in survivors of 30-40%. Rates of Hib pneumonia in developing countries have been estimated to be 2-5 times higher than rates of Hib meningitis. Countries using Hib vaccine in national immunization programs have virtually eliminated Hib disease; however, Hib disease continues to occur in countries that do not use Hib vaccines widely(2).

Recent studies assessing the difference in disease incidence between vaccinated and unvaccinated groups (called "probe studies") have demonstrated a high burden of Hib disease in South and Southeast Asia. For example, a Hib vaccine probe study in

Indonesia showed that the rate of bacterial meningitis prevented by Hib vaccine was 67 per 100,000 children <2 years of age(3). Surveillance studies in South Asia have shown high burden of Hib meningitis(3). In Pakistan, of 237 children with probable bacterial meningitis, Hib was detected in the CSF of 45 children (18.9%). In this study, the minimum detected incidence rate of Hib meningitis in the metropolitan region of Hyderabad and its surrounding population was 7.6 per 100,000 (95% CI: 4.29, 12.59) in children <5 years of age and 38.1 (95% CI: 22.35, 61.4) per 100,000 in children <1 year of age(4). In Sri Lanka, a surveillance study done in 2004 showed that the rate of Hib meningitis was 20.1 (95% CI: 14.5, 27.8) cases per 100,000 children <5 years(5).

### *Hib Disease in India*

Hib disease has been shown to be a significant cause of morbidity and mortality in Indian children <5 years of age, particularly those in the poorest communities. Hospital-based studies in India have shown that Hib and pneumococcus were the most common causes of childhood bacterial meningitis; however, these types of studies do not provide population based disease incidence(6,7,8). A multi-centre study from Jaipur, Jodhpur, Delhi and Kolkata found that 0.5-2.6% of all hospital admissions were attributable to bacterial meningitis, including Hib(9). Studies that tested cerebrospinal fluid (CSF) using other sensitive laboratory techniques such as latex agglutination testing (LAT) or counterimmune electrophoresis (CIE) along with culture found that 25% (range: 14-35%) of bacterial meningitis was attributable to Hib in India (**Table I**)(10-14).

Indian studies have reported case fatality rates of Hib meningitis of 20-29%(8-10,15), while all invasive Hib disease (including meningitis) had a case fatality rate of 16%(8). In addition, neurological sequelae are common among children who survive Hib meningitis. Researchers in Pune followed 14 Hib meningitis cases and found that 5 (36%) survivors had at least one neurological sequelae, including persistent seizures (18%), isolated hearing loss (27%), and moderate to severe developmental delay (9%)(10). A recent study in Chandigarh demonstrated that 40% of children with acute

**TABLE I** PROPORTION OF MENINGITIS CAUSED BY HIB

Author/year	Syndrome	Age range	Study Site	Study Size	% Hib positive
Deivanayagam, <i>et al.</i> 1993(11)	suspected meningitis	2 mo - 11 y	Chennai	114	25
Singhi, <i>et al.</i> 2002(13)	suspected meningitis	1 mo - 12 y	Chandigarh	107	35
Suvarna Devi, <i>et al.</i> 1982(14)	acute meningitis	<15 y	Behrampur	70	19
Mani, <i>et al.</i> 2007(12)	bacterial meningitis	<5 y	Bangalore	51	14
Chinchankar, <i>et al.</i> 2002(10)	bacterial meningitis	1 mo - 5 y	Pune	54	26

*Studies using culture, latex agglutination, counter immunoelectrophoresis and/or PCR.*

**TABLE II** PROPORTION OF ACUTE LOWER RESPIRATORY INFECTIONS CAUSED BY HIB

Author/year	Syndrome	Age range	Study Site	Study Size	% Hib positive
Bahl, <i>et al.</i> 1995(18)	Severe and very severe pneumonia	<5	Delhi	110	19
Kumar, <i>et al.</i> 1984(19)	Lobar pneumonia and empyema thoracis	<11	Chandigarh	64	13
Patwari, <i>et al.</i> 1996(20)	Pneumonia and bronchopneumonia	<12	Delhi	132	15

*Studies using culture with latex agglutination, counter immunoelectrophoresis and/or PCR.*

**TABLE III** PREVALENCE OF NASOPHARYNGEAL CARRIAGE AMONG HEALTHY CHILDREN IN INDIA

Author/year	Age range	Study Site	Detection Method	Study Size	Hib Positive	% Hib positive
Das, <i>et al.</i> 2002(15)	5-12 y	Delhi	culture	566	N/A	16.3*
ICMR(22)	Infants<2 y	Chandigarh, Kolkata, Vellore	culture	1114	76	6.8
Sekhar, <i>et al.</i> 2008(21)	0-24 mo	Chandigarh	culture	1000	77	7.7

*\*projected based on a subset of Hi typed as Hib*

bacterial meningitis had sequelae at 12 months of follow-up(16). Another study in Kottayam found that 23% of the children surviving acute bacterial meningitis after treatment had developmental delay and 20% had mental retardation(17).

A review of available data showed that Hib is also a leading cause of pneumonia in India. Indian studies of the etiology of pneumonia using some non-specific methodologies such as nasopharyngeal (NP) swab collection in addition to lung fluid taps – tested using a combination of sensitive techniques (LAT, CIE, and/or polymerase chain reaction (PCR)) in addition to culture found Hib to be responsible for between and 13-19% of pneumonia and lower lung disease (**Table II**)(18-20).

Based on a systematic analysis of local and regional data that met specified quality parameters, a mathematical model devised by the World Health Organization and vetted by experts estimated the burden of Hib disease in India in the year 2000 to be about 2.4 million cases and 72,000 deaths in children <5 years of age, accounting for approximately 4% of all child deaths in India (WHO; In press).

#### **Nasopharyngeal Carriage**

Hib carriage among infants was found to be common in India (**Table III**), with an estimated prevalence of 7.2% (range 6.8-16.3%)(21,22), which is consistent with regional data. Studies have shown carriage prevalence of 4-7% in Turkey, Thailand, and Vietnam(23-25).

Hib carriage rates increase throughout infancy and into the second year of life, peaking at age 18-21 months at a prevalence of 20.3%(21). The likelihood of carriage has been shown to increase if the child's parents were illiterate, if they lived in a katcha (mud/thatch) house, or if they lived in crowded conditions(21).

### ***Antibiotic Resistance***

Antibiotic resistant strains of Hib are common across India, and resistance to all major antibiotics used in India has been described. Reports of prevalence of resistance of Hib to ampicillin range from 15.0% to 60.4%(6,26-28). Similarly, rates of resistance against several other antibiotics, including third generation cephalosporins, chloramphenicol, cotrimoxazole and erythromycin, ranged from 3% to 67%(6,7,15,26-28).

## **HIB VACCINES**

### ***Safety***

Globally, millions of doses of Hib vaccine have been administered in the last 2 decades, and have been found to be extremely safe. Studies, both published and unpublished, that have been done on Indian Hib vaccines were presented at the meeting. One study reported rates of solicited general symptoms (fever, irritability, drowsiness, loss of appetite) following inoculations of 0.8%(29). Other studies reported that there were no significant adverse reactions associated with Hib vaccination(29-32).

### ***Efficacy and Immunogenicity***

Hib vaccine has been shown to be >95% efficacious in diverse populations around the world. The efficacy of Hib vaccines was demonstrated in numerous clinical trials in Europe, the US, and The Gambia. In the mid 1990's, a large vaccine trial was conducted in The Gambia, comparing Hib vaccine mixed with diphtheria-tetanus-pertussis (DTP) to DTP alone. This trial showed a protective efficacy of 95% (95% CI: 67-100%) against all invasive Hib disease after three doses(33). Experts agree that it is

no longer ethical to conduct randomized clinical trials to demonstrate the clinical efficacy of Hib vaccine, since this has been demonstrated in a wide variety of settings; based on available immunogenicity data there is no reason to suspect that efficacy will be any different in India.

Hib vaccine has nearly eliminated Hib disease in all developed and developing countries where it has been introduced(2). Recent studies in Kenya and Uganda showed dramatic reductions in Hib disease rates after Hib vaccine was introduced into each country's routine immunization program(34,35). One example from South Asia is a case-control study in Bangladesh which showed that 3 doses of Hib conjugate vaccine reduced rates of laboratory confirmed meningitis by 90% and radiologically confirmed pneumonia by 16-32%(36).

Numerous immunogenicity studies have been performed in India, and have shown that all of the vaccines tested are highly immunogenic. Seropositivity after vaccination, as defined by antibody concentration of >0.15 µg(37), was 100% in all Indian studies(30-32). Furthermore, combination vaccines have proven highly immunogenic. Both DTwP/HepB/Hib combination vaccine(29) and Hib vaccine combined with locally produced DTwP(31) proved as immunogenic as single antigen Hib vaccines.

### ***Herd Effect***

Hib vaccines have been shown to induce significant "herd effect" in both developed and developing country settings; that is, immunizing a proportion of the population reduces disease in unimmunized children living in the same community. Several studies have shown a substantial herd effect with the introduction of Hib vaccine(38-41). In Gambia, Hib vaccine was introduced in the mid-1990s, but vaccine supply was interrupted at times and coverage with 3 doses of vaccine ranged from 62% to 75%. Nevertheless, carriage rates in unvaccinated children fell from 7.7% to 3.8%, and invasive Hib disease has virtually disappeared(42,43). Therefore, a population does not have to be fully vaccinated in order for substantial benefit to be seen.



### ***Expert Recommendations***

Both Indian and international expert committees have recommended the use of Hib vaccines. WHO issued a position statement that all countries should introduce Hib vaccine, and that “the lack of local surveillance data should not delay the introduction of the vaccine especially in countries where regional evidence indicates a high burden of disease”(44). The Indian Academy of Paediatrics also issued a statement in 2004 that “Hib vaccine should be offered to all children”(45).

### ***Vaccine Supply and Presentation***

Hib vaccines are available in several formulations: monovalent, tetravalent (DTwP-Hib), pentavalent (DTwP-HepB/Hib), and in similar combinations with acellular pertussis vaccine. At the time of the meeting, three pentavalent, 2 tetravalent and 4 monovalent Hib vaccines from Indian manufacturers were licensed in the country, and an additional 6 pentavalent and 3 monovalent vaccines were in development. Two Indian pentavalent vaccines (liquid) in addition to 2 imported vaccines (1 liquid, 1 lyophilized) had been prequalified by the WHO and are available through UNICEF procurement. A third Indian lyophilized formulation is expected to be prequalified in the next year. The vaccines are available in a variety of vial sizes. Prequalified pentavalent vaccines are available in single, two and ten-dose presentations.

Indian manufacturers currently produce 4 million doses of Hib-containing vaccines each year for the private market, although installed capacity (ability to produce given sufficient lead time) is significantly higher at an estimated 70 million doses per year. Pentavalent vaccine supply offered to GAVI-eligible countries from two multi-national suppliers is currently 66 million doses per year; potential capacity is significantly higher. Supplier capacity would be sufficient to meet the present and future demand for India if given sufficient lead time to increase production.

### ***Immunization Schedule***

Hib vaccination fits into the UIP immunization schedule. The earliest age when vaccination can be

given is 6 weeks, with a minimum gap of 4 weeks between each dose. The recommended ages for vaccination (6, 10, and 14 weeks) which corresponds with the UIP schedule for oral polio, DwPT and hepatitis B vaccines.

### ***Cost-effectiveness***

Hib vaccines have been demonstrated to be highly cost-effective. A recent study in Kenya showed that the cost per discounted death averted was US \$1,197(46), and a study from Indonesia concluded that the cost per death and per discounted Disability Adjusted Life Year (DALY) averted was US\$ 3,102 and US \$74, respectively(47). In the Indonesian analysis, it was estimated that Hib vaccine would prevent 4.9% of the current under-five mortality.

A preliminary cost-effectiveness analysis from India, using the WHO disease burden estimates for India, suggests that Hib vaccine introduction into the UIP is highly cost-effective. This analysis indicates that, with conservative burden of disease assumptions and the 2008 UNICEF price of US \$3.60 per Hib vaccine dose, the costs per DALY averted is US \$254 (Ms Ulla Griffiths, personal communication, 2008). Based on trends of other vaccines in national programmes, prices would be expected to decline significantly from current levels. With a price of US \$2.00 per dose of pentavalent vaccine, the cost per DALY averted will be US \$26. In 2007, the GDP per capita in India was US \$785. Hence, the costs per DALY averted from Hib vaccine is estimated to be considerably less than the GDP per capita and according to WHO benchmarks, the vaccine is therefore considered “highly cost-effective”.

### **PROGRAMMATIC CONSIDERATIONS**

The committee also considered programmatic issues in the context of adding new vaccines to the UIP, including logistic issues such as training, vaccine supply, cold chain capacity, and financing. The committee considered country-wide vs. phased introduction. The committee also considered that 11 states had already introduced or were soon to introduce Hepatitis B vaccine as part of Phase II of Hepatitis B vaccine introduction plan. Since

pentavalent vaccine contains Hepatitis B, the committee considered this to be an opportunity to harmonize the introduction of Hib with Hepatitis B vaccine. Although a detailed assessment of vaccine-associated adverse event surveillance, disease surveillance, and UIP capacity were beyond the scope of this meeting, it was pointed out that such issues need to be considered simultaneously with new vaccine introduction. The committee also felt that the introduction of this vaccine even in low-performing states with <60% DTP vaccine coverage will have substantial impact on reducing Hib disease burden because of the herd immunity induced by the vaccine.

### RECOMMENDATIONS

Based on the above considerations, the committee came to the following conclusions and recommendations regarding introduction of Hib vaccine in India:

1. There is sufficient evidence of relatively high Hib disease burden in India to warrant the early introduction of Hib (conjugate) vaccine into the UIP with a goal of national coverage by 2012.
2. As simultaneous nationwide roll-out will be logistically challenging, Hib should be introduced in a phased manner beginning as soon as possible.
3. The pentavalent vaccine should be introduced initially in at least the 11 states that are currently part of Phase II of Hepatitis B vaccine introduction. In addition, states with high under-5 mortality such as Uttar Pradesh and Bihar should be considered for introduction of the pentavalent vaccine as soon as possible, at least in some districts as part of the first phase of introduction in those states. Even though these states have relatively poor immunization coverage, the introduction of this vaccine is likely to protect large number of children both by the direct effect on immunized children and by the "herd effect" on those who are not immunized.
4. The preferred formulation is the liquid pentavalent since it will eliminate the need for administering an additional injection, simplify the delivery of vaccine in the field, and reduce the training requirements and supplies. Vial size should be determined by programmatic considerations such as cold chain and projected wastage.
5. To monitor trends in disease and carriage reduction, and to evaluate the potential future need for a booster dose (as evidenced by disease occurrence in older age groups), it is critical to establish ongoing surveillance for invasive bacterial diseases prior to and post vaccine introduction.
6. Research activities should be coordinated by the Indian Council of Medical Research (ICMR) in collaboration with other agencies such as Department of Biotechnology (DBT). A coordination plan should be developed within 6 months. A research subcommittee should be formed to oversee the scientific issues involved with vaccine introduction.
7. There should be an assessment of joint introduction of pneumococcal and Hib vaccines in a high mortality area to assess impact of these vaccines on mortality reduction, as both are effective against bacterial meningitis and pneumonia, two conditions with high case-fatality.
8. The committee recommends strengthening the system for disease surveillance, vaccine safety monitoring and program monitoring within UIP, which will coordinate with the research subcommittee.
9. To optimize the success of Hib vaccine introduction, the committee recommended that sufficient resources (personnel, material and design) be put into the UIP system to ensure a transformational change, not merely an incremental change. A separate mechanism (including a dedicated committee) should be formed to review and define the needed human resources at the central, state, district, and local levels for optimal UIP performance.

**SUMMARY**

Hib vaccine has the potential to prevent over 70,000 child deaths and significantly more cases of illness and disability every year in India. Children of families who could afford the vaccine have been receiving it for several years in private medical care setting. Recognizing that it is the poorest children that are most at risk of disease, as well as vulnerable to serious adverse consequences, the Indian Academy of Pediatrics and the WHO have recommended that all children be offered the vaccine.

Subsequent to the presentation of these recommendations, NTAGI in its July 2008 meeting not only endorsed them but also resolved to recommend to the Government of India that Hib vaccine should be introduced in all states as early as feasible. Although implementation will be a challenge given the strains on the current system, the government officials have made a commitment to put the resources into the system necessary to make Hib vaccine available to all Indian children as quickly as possible. The case for adoption of Hib vaccine in the UIP is clear; to help India make progress towards combating a large but preventable burden of disease and reducing antibiotic resistance that increases healthcare cost and health risk for children who may get Hib disease. Indian suppliers now contribute to meeting global demand for the vaccine and the additional supply and competition should help contribute to the trend of making Hib vaccine less expensive than at present. It is now time to begin adopting the vaccine in UIP. To help move the adoption of vaccine closer to reality, the GAVI Alliance has offered the opportunity to apply for funding to help adopt new vaccines and to strengthen the immunization system. The government's commitment to the health of all children in India is an integral part and important step in reaching India's health goals and addressing issues of inequity as it prevails now.

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#### Appendix I List of Participants

**Sub-committee members:** JPMuliyil, CMC Vellore - Chairperson; MK Bhan, Secretary, DBT; SK Bhattacharya, Additional DG-ICMR; Lalit Kant, Head, ECD, ICMR; NK Arora, Executive Director, INCLIN Trust; M Santosham, Johns Hopkins University; Thomas Cherian, WHO HQ, Geneva; Ashok Dutta, New Delhi; Jacob John, Vellore – Co-Chair NTAGI; Hamid Jafari, National Polio Surveillance Unit; Naveen Thacker, Indian Academy of Pediatrics representative; Padmanaban, Tamil Nadu Health Services; M Senthilmazhan, Saradha Suresh and Ambujam Nair Kapoor, ICMR.

**Special Invitees:** Andrew Clark, London School of Hygiene and Tropical Medicine; Rana Hajjeh, Hib Initiative; Anuradha Bose, Christian Medical College, Vellore; Rajesh Kumar, PGIMER, Chandigarh; Meredith Shirey, UNICEF; Lois Prevor Drumm, Johns Hopkins University; Aruna Chandran, Johns Hopkins University, and SD Khaparde, DC Immunization, MOHFW.

**Partner agencies:** Sanjeev Upadhaya, USAID; Krishna Rao, Public Health Foundation of India; Syed Abbas, Public Health Foundation of India; R K Agarwal, President, Indian Academy of Pediatrics; Ajay Gambhir, Indian Medical Association; Soren Spanner, UNICEF; Satish Gupta, UNICEF; Sunil Bahl, NPSU; Rajeev Gera, NPSU; Pem Numgyal, WHO SEARO; Paul Francis, WHO India; Chandrakant Lahariya, NPSU; Shamila Sharma, NPSU; Harish Kumar, UNICEF, and Tim Peterson, NPSU.

*Appendix 2* Data Reviewed During Subcommittee Process

Subject	Data reviewed
<i>Hib Disease burden and Epidemiology</i>	
Incidence	Batuwanthudawe unpublished(5), Cherian (personal communication), Gessner 2008(47), John 1998(6), Zaidi in press(4)
Nasopharyngeal carriage	Das 2002(15), ICMR 2008(22), Oguzkaya-Artan 2007(23), Olsen 2005 (24), Sekhar 2008(21), Tran 1998(25)
Pneumonia and respiratory infections	Bahl 1995(18), Kumar 1984(19), Patwari 1996(20), Puri 1999(24)
Meningitis	Chinchankar 1998(10), Deivanayagam 1993(11), IBIS 2002(8), ICMR 2008(22), Kabra 199(19), Mani 2007(12), Singhi 2002(13), Suvarna Devi 1982(14).
Sequelae	Chinchankar 1998(10), Singhi 2007(16).
Case fatality	Chinchankar 1998(10), IBIS 2002(8), Kabra 1991(9), Steinhoff 1998(7)
Antibiotic use and resistance	Das 2002(15) , Jain 2005(27), John 1998(6), Mani 2007(12), Puri 1999(26), Singhi 2002(13), Steinhoff 1998(7)
<i>Hib Vaccine</i>	
Safety, immunogenicity, efficacy, and impact	Acharya 1997(32), Adegbola 1998(42), Adegbola 2005(43), Baqui 2007(36), Bavdekar 2007(30), Cherian 2002(31), Cowgill 2006(34), Gallo 2002(38), Gessner 2005(3), Jain 1997(27), Kayhty 1983(37), Kumar 1997(29), Lee 2008(35), Makela 2003(40), Moulton 2000(41), Mulholland 1997(33), Perdue 2000(39), Watt 2003(2)
Cost effectiveness	Akumu 2007(46), Gessner 2008(47), Griffiths (personal communication)