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The status and need for a safe and affordable dengue vaccine in India

Report from the PlantVaccine project

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Summary:

Dengue is the most rapidly spreading mosquito-borne viral disease in the world, with an estimated 50 million infections occurring annually. Dengue infections are a significant cause of morbidity and mortality and lead to adverse social and economic impacts in many developing tropical countries. Dengue is a matter of much concern in India, where dengue is now re-emerging as one of the most important public health problems. Currently no vaccine has been licensed. The PlantVaccine project aims to develop a plant based vaccine candidate for dengue fever. This report reviews the status of and need for a dengue vaccine, easy accessibility and affordability, and overall social and economic implications of such a vaccine development in India.

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Preface

This report is part of the PlantVaccine project: Expression and evaluation of envelope domain III-based experimental tetravalent dengue vaccine using a tobacco chloroplast expression system. The project is funded by the Research Council of Norway.

The aim of the PlantVaccine project is to develop a new experimental vaccine candidate against dengue, using the chloroplast expression approach to develop vaccine antigens using the tobacco plant. The project focuses on establishing a cost-effective system for large scale production of a dengue vaccine, ensuring a safe and affordable vaccine for end users.

This report is a macro level review of the status of dengue fever and the need for a safe and affordable dengue vaccine in India, which can reach poor and disadvantaged groups. It reviews the possibilities of a plant based vaccine and its implications if introduced in India.

Project website: www.bioforsk.no/plantvaccine

Content

1. Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. An estimated 50 million dengue infections occur annually (WHO, 2009). Dengue infections are a significant cause of morbidity and mortality and lead to adverse social and economic impacts in many developing tropical countries. Cases reported to the World Health Organization (WHO) over the past four decades show an upward trend, partly resulting from an increased spread of vector mosquitoes and increase in total human population, including specific increases in urban populations at risk of dengue infection.

Dengue is endemic in the South East Asian region and is a leading cause of hospitalization and death among children in several countries in the region (WHO, 2010). Dengue affects all strata of the population, but flourishes in urban slums and poor peri-urban areas. Dengue is a matter of much concern in India, especially to low income groups, who do not have timely access to medical and diagnostical facilities and due to inadequate mosquito control.

This report reviews the status of and need for a dengue vaccine, easy accessibility and affordability, and overall social and economic implications of such a vaccine development in India. The PlantVaccine project (www.bioforsk.no/plantvaccine) aims to develop a new experimental tetravalent vaccine candidate against dengue, using the chloroplast expression approach to develop vaccine antigens using the tobacco plant. The project focuses on establishing a cost-effective system for large scale production of a dengue vaccine, ensuring a safe and affordable vaccine for end users.

2. Spread and global burden of dengue

2.1 Dengue fever and spread

Dengue fever is an acute mosquito- transmitted disease, which causes a usually mild but debilitating viral fever (breakbone fever), and is prevalent throughout the tropics, where the urban-dwelling mosquito *Aedes aegypti* is a major vector. There are four known dengue viruses or serotypes. Most primary infections cause a debilitating, but nonfatal, form of illness. Some patients, particularly children, experience a more severe and occasionally fatal form of the disease, called dengue haemorrhagic fever, the most severe form of which is referred to as dengue shock syndrome (WHO 2006).

Dengue is a rapidly growing problem in tropical and subtropical countries where the majority of the world`s population resides. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South and South East Asia and the Western Pacific (WHO, 2009). Dengue has been re-emerging in the last decades; with an estimated 50- 100 million people infected annually, it is now considered the most rapidly expanding arboviral disease in the tropics and subtropics. It is estimated that 2.5 billion people (including 1 billion children) are at risk of dengue fever and the life threatening disease, severe dengue (Webster et al, 2009; WHO, 2009). In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. Not only is the number of cases increasing as the disease is spreading to new areas, but explosive outbreaks are occurring. The virus periodically causes acute, widespread epidemics, such as in 1998 when 1.3 million cases of dengue fever and DHF and over 3500 deaths were reported from Latin America, the South-East Asia Region and the Western Pacific Region (WHO, 2006). More recently, in 2004, an outbreak was reported from Indonesia with more than 650 deaths. The burden of severe disease remains proportionately much greater in Asian and Pacific countries although it considerably increased in recent years in the Americas. There is also an increase of dengue in its more serious forms, such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), for reasons that are not fully understood. In addition to 50 -100 million cases of dengue fever each year, WHO has estimated that there are 500 000 cases of DHF/ DSS and that more than 20 000 deaths occur each year (WHO, 2006). The severe forms, have become an increasing cause of morbidity and mortality, and are straining the health care systems of many endemic countries. Studies have shown that dengue fever and dengue haemorrhagic fever has a total impact of the same order of magnitude as many of the major infectious diseases such as malaria, tuberculosis and others (Gubler, 2002).

The factors considered responsible for global resurgence of dengue fever and its more severe forms are unprecedented population growth, unplanned and uncontrolled urbanization, increased air travel, absence of an effective mosquito control programme and deterioration of public health infrastructure (Chaturvedi & Nagar, 2008; Hombach, 2007). Dengue transcends international boundaries and is emerging rapidly as a consequence of globalization, rapid unplanned and unregulated urban development, improper water storage and unsatisfactory sanitary conditions. Climate change and global warming add yet another challenge for dengue control.

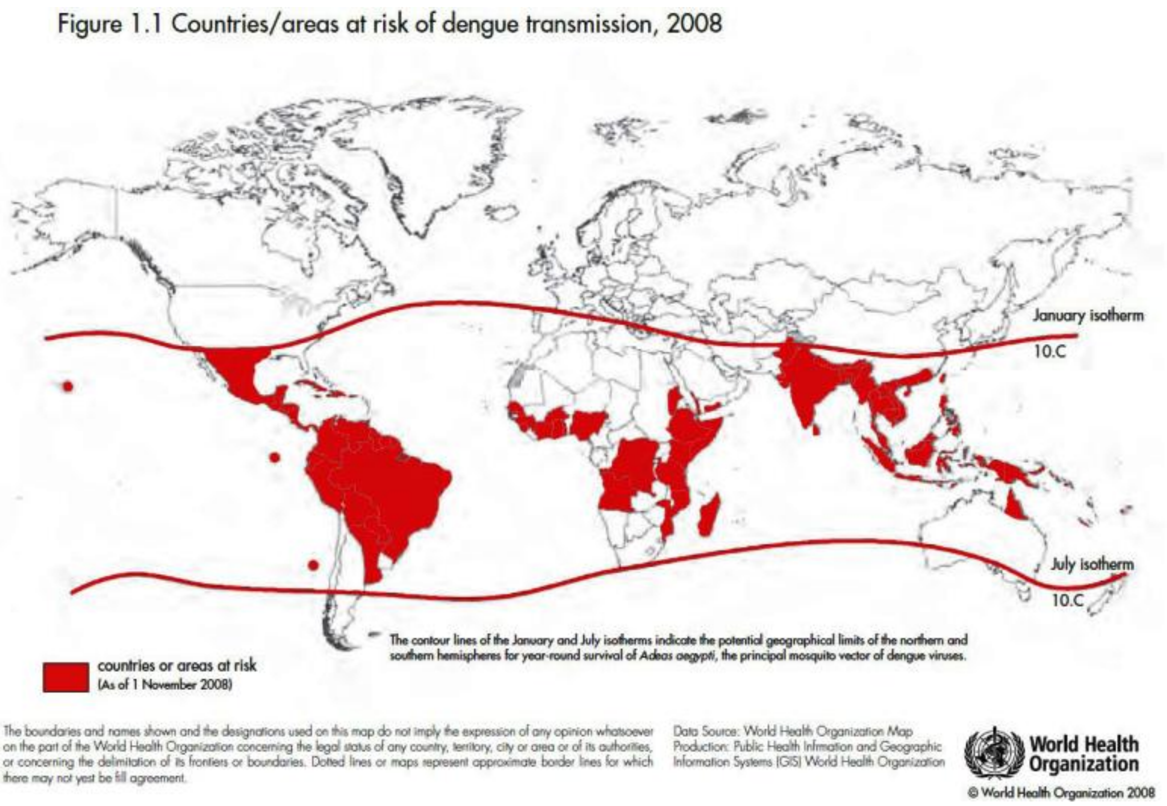

Fig.1. Countries/areas at risk of dengue transmission. Source: WHO, 2008

2.2 Economic and social impact of dengue

Dengue inflicts a significant health, economic and social burden on the populations of endemic areas.The social impact of the disease is significant. The illness can cause significant stress for patients and their families, as their lives are disrupted. It can create a psychological burden for families, as well as a financial burden due to absence from work and increased expenses. Dengue may also selectively affect the poorest communities in a society, due to community social and cultural practices and infrastructure. Increasing urbanization typically attracts the poor to periurban settlements with deficient water supplies and unsatisfactory sanitary conditions that favor the expansion of the vector. Dengue, along with other neglected tropical diseases, is associated with poverty and typically affects low-income and politically marginalized people living in urban and rural areas (WHO, 2010).

Dengue imposes a large cost to the society in endemic countries, both direct and indirectly. Direct costs within the health-care system comprise of the cost of diagnosis, treatment and prevention of dengue, as well as surveillance and monitoring of outbreaks, cases and deaths. Indirect costs are the economic value lost by households and society in general owing to illness and premature mortality of dengue patients and productivity losses of household members and friends affected (Suaya et al, 2007). This is in addition to the costs incurred for treatment of household members affected, in particular poorer sections of the society. Especially during epidemics of dengue, costs to society increases and health systems in endemic countries can become rapidly overburdened.

A recent study conducted by Suaya and others (2009), showed that the economic cost of dengue fever was at least $1.8 billion yearly, in the eight countries included in the study, giving an indication to the very heavy economic burden of the disease to the health system and society in endemic countries. For Southeast Asia, Shepard and others (2004) estimate individual treatment costs of US$139 for dengue haemorrhagic fever and US$4.29 for dengue fever (including health clinic visits, hospitalization, medications, travel expenses, and parents' time seeking treatment for their children). This estimate implies annual costs in the region of US$69.5 million—US$105 million for dengue haemorrhagic fever and US$35.5 million for dengue fever. Additional economic losses are expected because of the impact of dengue outbreaks on tourism.

A number of studies have attempted to estimate the burden of dengue. The burden of illness caused by dengue refers to the amount of disease imposed by dengue and can be measured using a set of epidemiological indicators, such as number of clinical cases classified by severity, duration of the illness episode, quality of life during the illness episode, case-fatality rate, and absolute number of deaths during a period of time (Suaya et al, 2007). Indicators often used in such studies include quality-adjusted life years (QALY) or disability-adjusted life years (DALY). The burden imposed by dengue and the potential benefits of any intervention, such as vaccination, can then be expressed in terms of DALYs lost or saved and cost per DALY lost or saved.The Disease Control Priorities Project published the global burden of disease for 2001 to 2003. It estimated the global burden of dengue as 528 000 DALYs for the year 2001. This corresponds to a burden of 264 DALYs per million population per year for the more than two billion people living worldwide in areas at risk of dengue (WHO, 2009). Current global estimations of the burden of dengue are considered to be uncertain because of a number of factors, such as the under-reporting of dengue cases (Suaya et al, 2007). New and unpublished data from the Pediatric Dengue Vaccine Intiative indicates that the global burden of dengue is much greater than previously estimated (PDVI, 2010). There is no doubt that dengue fever imposes a large burden to endemic countries and that new prevention efforts are urgently needed.

3. Implications of a dengue vaccine in India

3.1 Dengue burden, current control measures and demand for a vaccine

In India, dengue is now re-emerging as one of the most important public health problems with many outbreaks reported in different areas during the past four decades. It represents a large problem in India with its huge population of more than one billion people, poor medical and diagnostical facilities, inadequate mosquito control and many on the ground conditions that favor expansion of the vector. Increasing numbers of people in India live without access to good housing, clean water, sewage and waste management systems, which increases exposure to mosquito vectors that transmit dengue and other diseases. Dengue is considered to be a predominantly urban disease, but outbreaks are now increasingly reported in rural areas, implying that the population at risk is increasing (Chaturvedi& Nagar, 2008). Thus environmental conditions such as sanitation, water availability, proximity to hospitals and weather parameters influence the spread and impact of dengue to a large extent.

The surveillance of dengue in India has been very limited and studies have shown that gaps in epidemiological data and surveillance mean that the burden of dengue in India is uncertain (Suaya et al, 2007). Due to weak case surveillance, small outbreaks have gone unreported and the number of cases and deaths reported are mainly from the capital. Dengue has existed in India for a long time, but DHF was first reported in 1963. Since then several outbreaks of dengue fever has been reported, with the first full blown epidemic of the severe form of the dengue illness in North India in 1996. In Delhi, during the 1996 epidemic, 10 252 cases and 423 deaths were reported. Delhi maintains high vulnerability due to international tourist traffic and the extensive breeding potential of vector, Aedes aegypti. Delhi recorded epidemics of dengue fever during the years 1967, 1970, 1982, 1988, 1991, 1992 and 1996 (Singh, 2007). In the year 2001, there were 3,306 cases with 53 deaths; in 2002, the number was 1,926 cases and 33 deaths. In 2003, there was a huge outbreak with 12,754 cases and 215 deaths. Another large outbreak came in 2006, with an estimate of 10,344 cases and 162 deaths due to severe forms of dengue. New data from the National Vector Borne Disease Control Program in India have reported 7262 cases of dengue fever and 25 deaths in 2010 (NVBDCP, 2010 a). Especially during epidemics, developing countries like India faces considerable economic losses due to dengue. Garg and others (2008) have estimated the total economic burden of the 2006 epidemic to be approximately US$ 27.4 million. Their estimates include loss of workdays and productivity due to the illness. The report was an initial attempt to quantify the growing economic consequences of regular dengue epidemics in India and gives an indication of the stress dengue puts on both the public and private sector in India.

The Government of India (GoI) developed a long term action plan in 2007, for prevention and control of dengue and another vector borne disease, chikungunya. The plan focuses on diagnosis, treatment and control of the diseases and is aimed at strengthening early case reporting and management, integrated vector management and also includes supporting interventions such as behavior change communication. According to the action plan, the GoI has also established surveillance hospitals and laboratories with diagnostic facilities (NVBDCP, 2010 b). However, these plans have failed to reduce the public health burden of dengue to an acceptable level due to low awareness of people and absence of prevention measures.

Primary prevention of dengue is currently possible only with vector control and personal protection from the bites of infected mosquitoes. According to the National Vector Borne Disease Control Programme (2010), the current vector control measures in India are; personal prophylactic measures (such as use of mosquito repellent), biological control (such as use of larvivorous fishes in ornamental tanks, fountains etc and use of biocides), chemical control (such as use of chemical larvicides like abate in big breeding containers and aerosol space spray during day time), environmental management and source reduction methods (such as detection & elimination of mosquito breeding sources, management of roof tops, porticos and sunshades, proper covering of stored water, reliable water supply, observation of weekly dry day), health education (spreading knowledge to people regarding the disease and vector through various media sources) and community participation (sensitizing and involving the community for detection of Aedes breeding places and their elimination). During outbreaks, emergency vector control measures can also include broad application of insecticides as space sprays, however this has shown to be variable in its effectiveness and the procedure is costly and operationally difficult. According to WHO (2009), the application of vector control measures is frequently insufficient and ineffective. There are currently no available estimates of the costs of dengue vector control in India, but according to Shepard and others (2004), average annual costs for dengue vector control per 1,000 population were US$15 in 1998 in Indonesia and US$188 in 1998 in Thailand, US$240 in 2002 in Malaysia, and US$2,400 in 2000 in Singapore.

Studies have indicated that there is a high demand for a dengue vaccine in the South East Asian region, due to fear of the disease and difficulties in controlling it by using vector control measures. A study in four South East Asian countries from 2003 (DeRoeck et al) found that policymakers in this region were very concerned about the importance of and the urgent need for a dengue vaccine. The expenses and short term impact of control measures were cited by informants in the study and also a ranking of vaccines as the most important means of controlling dengue. The major concerns cited by policymakers and informants were that the vaccine should be safe and provided at a low cost. The study showed that there was a high population awareness of and concern about dengue and also a strong acceptance of and demand for vaccines in general among the populations in these countries.The market demand was assessed to be large even if not provided free through the government sector, but also at a low cost in public sector and in the private market. A recent study by Amarasinghe and others (2010) confirms that the highest demand for a dengue vaccine is in the public sector of dengue- endemic countries, such as India. This is also where the greatest public health impact will be, if a vaccine is introduced. Shepard and others (2004) reported that a pediatric dengue vaccine in South East Asia would be highly cost-effective and that a vaccine may be able to replace environmental control as a strategy for dengue prevention. The study`s results suggested that the potential sales of a dengue vaccine in South East Asia would be sufficiently large to support reasonable production costs and also make the vaccine available at an affordable price to the benefit of the poorer sections of the population, who are the most vulnerable group.

3.2 Introduction of a dengue vaccine in India

National policy decisions about new vaccine introduction relies on several factors, such as the disease burden, public pressure, the cost of new vaccines and the ability to incorporate them into existing vaccination programmes. If a safe, efficient and affordable vaccine for dengue fever becomes available, policymakers in India would need to consider these issues as well as considerations of financing for the vaccine and how to deliver it to its citizens.

Most vaccines in developing countries are delivered through public sector health care programs. In India, routine childhood vaccines are purchased and delivered through the public sector government channels and to a smaller extent through private markets outside the national immunization programme. India's Immunization Programme is one of the largest in the world in terms of quantities of vaccines used, numbers of beneficiaries, and the numbers of immunization sessions organized, the geographical spread and diversity of areas covered (GoI, 2005). Under the immunization program, six vaccines are currently used. The Universal Immunization Programme (UIP) is a national programme established in 1985, built upon the Expanded Programme on Immunization (EPI) started in 1978. The UIP is delivered as part of the Reproductive and Child Health (RCH) programme. All operational aspects of the UIP are funded by the Government of India. Funds are released to the states for disbursal to districts for logistics, cold chain maintenance, injection safety and payment of immunization- related staff (ibid). Immunization services in India are offered free in public health facilities, such as primary health centers, community health centers, hospitals and urban health services provided by municipalities. Despite rapid increases, the immunization rate remains low in some areas. India is a huge and diverse country, with a population of more than 1 billion people and 25 million new births every year, and the health infrastructure is unevenly distributed. Segments of the population whose health care needs are greatest often have poor access to health care due to economic, geographic and political constraints (GoI, 2005). The poorest and least influential groups, such as people in remote rural areas and in deprived urban settings, such as slums, are not always able to access health facilities. These areas and groups, if not treated properly, will further contribute to the spread of the disease, and also to casualities. Awareness raising in these groups is important, to prevent the occurrence and spread of the disease. Service and delivery of vaccines is also a challenge in India and where the immunization services do extend, there are some problems with communications failures and service breakdowns. Maintaining transport and refrigeration services is one challenge, as well as vaccine wastage, mal-distribution and poor forecasting. Immunization safety also remains a major problem, with problems of syringe and needle reuse, reconstitution practices, accidental needlesticks and waste mismanagement. The government has begun taking steps to improve healthcare, such as launching the National Rural Health Mission 2005-2012 in 2005, to provide effective healthcare to India's rural population, with a focus on states that have low public health indicators and inadequate infrastructure. Improving the urban primary healthcare structure has also been a focus of the government, following up on the goals of the National Health Policy of 2002 (GoI, 2002).

In India, a potential dengue vaccine would likely be introduced as part of routine early childhood immunization and potentially as a catch up immunization campaign for older children (Aamarsinghe et al, 2010). The vaccine could possibly be fully or partially covered by the government, with parallel programmes of free vaccination through EPI for certain groups (e.g children, people in rural areas) and sale of the vaccine at a reasonable price at a public sector facility to others (adults, urban residents, people in lower incidence areas etc). Internationally there are organizations such as The Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund that can assist India in introducing a new vaccine into the existing immunization programme. India is eligible to apply for subsidized introduction support from the GAVI Alliance. As with all new vaccines, the dengue vaccine would have to be carefully evaluated before being introduced into the EPI system. Criteria include appropriateness as a control strategy for the disease, efficacy and safety of the vaccine, compatibility with other antigens, adequate and affordable supply, and ability to be delivered. If the vaccine is to be used for infants, the dengue vaccination will need to be carried out on a schedule compatible with other vaccines. Interference between dengue vaccine and other vaccines likely to be given in the same time period must be ruled out. If the vaccine is to be delivered to older age groups, proper contact points will need to be established to deliver the vaccine effectively. In addition, vaccine presentation, packaging and stability requirements should be compatible with large-scale use. Owing to long distances, it would be useful to engage mobile units for vaccination to reach the communities located in remote areas. Certain vaccine characteristics could simplify the task of immunization and make it more affordable. If a dengue vaccine could be administered orally, not using needles, and without requiring a cold chain that could help ease immunization logistics such as delivery and storage. Local production of new vaccines is another approach that could lower price per dose and increase vaccine production capacity, as India is among the major buyers and makers of vaccines, locally as well as globally, and has traditionally aimed at self-reliance in vaccine technologies and production (Madhavi, 2005).

4. Vaccine development and potential benefits of a plant derived vaccine

4.1 Status of vaccine development

The most effective way to reduce disease and death from infectious diseases is to vaccinate susceptible populations. Despite this, more than 60 years after the discovery of the virus and start of systematic research into dengue vaccines, no dengue vaccine has yet been licensed (Hombach, 2007). The development of a vaccine has been hampered and delayed by the complex pathology of the disease, the need to control four viruses simultaneously, and insufficient investment by vaccine developers, due to low commercial interests (ibid). However, the continuing spread of the disease over the past years and increasing intensity of the disease, combined with new funding mechanisms for the development and use of vaccines for the developing world, have triggered renewed interest and investment in dengue vaccine research. The development of a vaccine offers the potential for effective prevention and long- term control of dengue infection.

There is no tested and approved vaccine for the dengue flavivirus; however there are several ongoing vaccine development programs. Among them is the Pediatric Dengue Vaccine Initiative set up in 2003 with the aim of accelerating the development and introduction of dengue vaccines that are affordable and accessible to poor children in endemic countries. Significant progress has been made in recent years and the pace towards clinical efficacy trials has accelerated substantially (WHO, 2009b). Several vaccine candidates are in phase I and II clinical studies and others are in advanced preclinical phase (PDVI, 2009). Several different strategies are being undertaken for the development of tetravalent vaccines against dengue. The main strategies applied are the traditionally and molecularly attenuated vaccines, chimeric live virus vaccines and DNA and recombinant subunit vaccines (Guzman et al, 2009). The vaccine candidates based on live viruses are in advanced stages of development and according to WHO (2009), two vaccine candidates have advanced to evaluation in human subjects in countries with endemic disease. Vaccines in early stages of development will benefit from the ongoing efforts aimed at better understanding the pathogenesis and give valuable input to the efforts towards a safe, efficacious and affordable vaccine.

4.2 Benefits of plant derived vaccines

WHO and other organizations have stressed the need for new technologies to create vaccines where the cost of delivery can be decreased, making the vaccines more affordable and more accessible to populations in developing and poor economies. In the last decade, plant biotechnology has emerged as a promising strategy that combines innovations in medical science with novel protein biomanufacture as a means to create affordable protein pharmaceuticals (Arntzen et al, 2005).The traditionally used approaches to vaccine development are very expensive and the demand for mass production at low cost has therefore made the plant-derived vaccine system an attractive alternative (Arntzen 2005; Daniell 2006; Bock 2007; Streatfield 2007). The currently used approaches to vaccine production are technologically complex and expensive and specialized requirements of packaging, cold chain and mode of delivery adds to the cost(Tiwari et al, 2009). Currently used mammalian cell line based vaccine manufacturing requires large investment and expertise. These factors limit their scale up and availability. Unlike the bacterial and mammalian expression systems, plants are ideal for the production of clean and safe vaccine antigens free of contaminants. There is minimized risk of contamination from potential human pathogens as plants are not hosts for human infectious agents (Arntzen, 2005). Plant based vaccines eliminate the need for expensive fermentation, purification, cold storage and sterile delivery. Extensive research has shown that a wide range of valuable proteins can be expressed efficiently in plants and in phase I clinical trials, several plant- derived vaccine antigens have been found to be safe and induce sufficiently high immune response (Tiwari et al, 2009). Plant systems are also more economic as they can be produced on a larger scale than industrial systems. Estimates suggest that it may become possible to obtain antigen sufficient for vaccinating millions of individuals from one acre crop (Tiwari et al, 2009). Other advantages of the plant based vaccines are convenient storage, elimination of health professionals for their delivery and the use of renewable resources for their production. Plant-based vaccine production systems could facilitate the production of a wide array of vaccines in a safe and easy-toscale- up manner with low production cost.

An extensive list of plant types have been used for expression of vaccine antigens, such as tobacco, potatoes, lettuce and tomatoes. The choice of plant species is important in that it determines how the vaccine will be applied. In recent years, plant- based novel production systems aimed at developing edible or oral vaccines have been discussed (Tiwari et al, 2009; Chebolu and Daniell, 2009). Edible vaccines would offer even more simplicity of use and lower cost, however there are still some challenges to developing such vaccines (Rybicki, 2010). In non- edible plants the vaccine antigen is extracted and purified before use. Antigen extraction is often performed when using tobacco, a plant that offers several advantages. Tobacco is a non-food and non-feed crop. Tobacco is also an excellent biomass producer (in excess of 40 tons of leaf fresh weight/acre, based on multiple cuttings per season) and a prolific seed producer (up to one million seeds per plant), thus hastening the time in which a product can be scaled up and brought to market. Tobacco is a self-pollinating crop and transgenes are maternally inherited when introduced via the chloroplast genome, i.e. the transgenes are not present in pollen, thus increasing biosafety of the genetically modified plants. To date, several vaccine antigens against bacterial, viral, or protozoan pathogens, as well as human therapeutic proteins, have been developed in transgenic tobacco chloroplasts (Daniell 2006; Bock 2007). These advantages and technical improvements have made tobacco chloroplasts an ideal and feasible plant factory for vaccine production.

4.3 The PlantVaccine approach

The PlantVaccine project aims to develop a vaccine against dengue fever that is safe and cost effective and that will be affordable to end users in developing countries, specifically focusing on India. A new experimental tetravalent vaccine candidate against dengue will be developed by engineering of tobacco chloroplasts to facilitate a cost effective production system. As mentioned earlier, there are several advantages in producing plant based vaccines through the chloroplast expression approach and the tobacco plant. Depending on the overall progress of the development of the tetravalent dengue vaccine candidate, a model will be developed to assess the cost effectiveness of the chloroplast expression system. The methodology we will employ will be a cost effectiveness analysis with a focus on benefits linked to accessibility and affordability of the vaccine.

Decisions regarding implementation of the use of a dengue vaccine will likely be based on the health and economic benefits of vaccination. Estimates of cost effectiveness are essential information for policymakers, as well as vaccine developers and funding agencies, and can help make better informed decisions on the inclusion of new vaccines in national immunization programmes.A cost-effectiveness analysis (CEA) compares the net health care cost with the improvement in health with or without vaccination.CEA is usually the method of choice in evaluating alternative health interventions because health decision makers are primarily interested to know what health improvements can be bought with a given budget and not the overall economic impact per se (Gold et al, 1996). CEA can be used to evaluate the relative efficiency of alternative interventions and can provide important information for assessing the potential implications of different vaccine candidates in terms of cost and health gains. Cost-effectiveness is often expressed in terms of cost per DALY (disability adjusted life year) gained, but it can also be expressed as cost per life-year, death, or hospitalization avoided.The concept of DALYs (disability-adjusted life years) was developed to enable the burden of individual diseases to be assessed quantitatively and comparatively.The number of DALYs assigned to a specific disease at a particular time gives an estimate of the sum of years of potential life lost due to premature mortality and the years of productive life lost (WHO, 2010).

Some preliminary studies have been done on the economic burden of dengue, but there are few studies on dengue health economics and cost effectiveness analysis of dengue vaccines (PDVI, 2010). However, literature exists on simulations of the cost effectiveness of vaccines for similar diseases, such as for malaria vaccines (e.g. Tediosi et al, 2009), and generally on cost effectiveness in health and medicine (Drummond et al, 2005; Gold et al, 1996), as well as the WHO guidelines for cost effectiveness analysis. These will be utilized to develop a model to assess the cost effectiveness of our experimental dengue vaccine. Data used will be on disease incidence, health care expenditures, vaccine coverage rates and vaccine efficacy, if estimates are available during the project period. A CEA also has to take into account, the socio-economic benefits, and not just cost effectiveness, especially in the context of developing countries, and this will be an important focus in the development of a model for assessing the experimental dengue vaccine candidate. Another aspect that would be interesting for further study are the determinants and economic impact (losses) of dengue fever in the affected areas in India (using univariate or multivariate analysis) or comparing the economic impact between affected and non affected areas (using a Chi-square analysis). However, this would require a good data set, from primary and secondary sources.

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