Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries

The adoption of new vaccines in developing countries can take at least a decade longer than in the West, highlighting the major disparities in drug and vaccine development for diseases affecting mainly the developing world.

The hepatitis B vaccine and *Haemophilus influenzae* type B conjugate vaccine have been used successfully in the West for more than 10 years, but are still relatively unused in developing countries. Lack of information on local disease burdens and questions of programme feasibility are only contributing factors — the main reason is that poor countries cannot afford to purchase the vaccines.

In sub-Saharan Africa, in the 10 years preceding 2001, there were more than 70 000 cases and 100 000 deaths from meningococcal disease, but no manufacturer was interested in developing a vaccine. In the UK, in contrast, three vaccine manufacturers developed a group C meningococcal conjugate vaccine in the same period.

In response to this problem, the public sector, governments and academic institutions have tried to encourage the development of new drugs and vaccines in the developing world by appealing to corporate altruism and providing incentives. But, vaccine development is costly, and the incentives have not proved enough. Typhoid and cholera are the only new vaccines to have been developed recently for diseases affecting mainly the developing world.

In 2000 the WHO commissioned an independent assessment of existing intellectual property on conjugation technology and costs of development and production for a group A or group A/C meningococcal conjugate vaccine for use in Africa.The results of this assessment together with a preliminary plan for introducing the vaccine in Africa were taken up by the Bill and Melinda Gates Foundation, who awarded a $70 million, 10-year grant to WHO and the Programme for Appropriate Technology for Health (PATH) to support the Meningitis Vaccine Project (MVP), with the goal of eliminating meningococcal epidemics in sub-Saharan Africa.

Two approaches were considered.The first was an alliance with an established vaccine manufacturer in an industrialised country, the second, technology transfer to a manufacturer in a developing country.

When the first approach was taken further, it was found that, even though the vaccine could be produced at less than $1 per dose, no industrialised vaccine manufacturer would undertake development because of the perceived opportunity costs of the project.

The authors then investigated the second approach. They identified a contract manufacturer in Europe that was willing to supply clinical-grade group A polysaccharide at low cost.They also identified several manufacturers in developing countries who were willing to provide high-quality tetanus toxoid at competitive prices. For development of the conjugation process, MVP contracted with a European biotechnology company with the expertise in the design, scale-up and technology transfer of glycoconjugate vaccines. Finally, MVP negotiated a contract with a large manufacturer in India for the final production of the vaccine.

The project is progressing well. As well as the low price, this approach offers other advantages. These are the development of a high priority product which substantially reduces internal competition with resources needed to complete other projects; and design of the product specifically for use in Africa rather than an adaptation of an existing product developed for use in premium-priced markets which are usually more expensive per dose.

While the challenges are substantial, if successful, this model offers several opportunities for development of other orphan vaccines at an affordable price for use in developing countries.

Jódar L, *et al.* Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries. *Lancet* Published online April 1, 2003. http://image.thelancet.com/extras/02art7254web.pdf

A cluster of cases of SARS in Hong Kong

Information on the clinical features of the severe acute respiratory syndrome (SARS) will be of value to physicians caring for patients suspected of having this disorder.

The authors abstracted data on the clinical presentation and course of disease in 10 epidemiologically linked Chinese patients (5 men and 5 women 38 - 72 years old) in whom SARS was diagnosed between 22 February 2003 and 22 March 2003, at their hospitals in Hong Kong, China.

Exposure between the source patient and subsequent patients ranged from minimal to that between patient and health care provider. The incubation period ranged from 2 to 11 days. All patients presented with fever (temperature >38°C for over 24 hours), and most presented with rigor, dry cough, dyspnoea, malaise, headache, and hypoxaemia. Physical examination of the chest revealed crackles and percussion dullness. Lymphopenia was observed in 9 patients, and most patients had mildly elevated aminotransferase levels but normal serum creatinine levels. Serial chest radiographs showed progressive air-space disease. Two patients died of progressive respiratory failure; histological analysis of their lungs showed diffuse alveolar damage.There was no evidence of infection by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or *Legionella pneumophila*. All patients received corticosteroid and ribavirin therapy a mean (±SD) of 9.6 ± 5.42 days after the onset of symptoms, and 8 were treated earlier with a combination of β-lactams and macrolide for 4 ± 1.9 days, with no clinical or radiological efficacy.

SARS appears to be infectious in origin. Fever followed by rapidly progressive respiratory compromise is the key complex of signs and symptoms from which the syndrome derives its name.The microbiological origins of SARS remain unclear.

(Tsang K, *et al. NEJM* 2003; **348:** 1977-1985.)

HDL concentrations relate to the clinical course of HIV viral load in patients on antiretroviral therapy

The object of the study was to determine whether levels of high-density lipoprotein (HDL) are associated with viral load response in HIV-treated patients, and to seek an explanation based on amino acid sequence similarity between the key apolipoprotein A1 and HIV proteins concerned in viral replication.

The major HDL lipoprotein is apolipoprotein A1, which is able to inhibit HIV-induced syncytium formation.This retrospective clinical study assessed the relationship between the response to antiretroviral treatment (time of undetectable viral load/duration of viral suppression below the limit of detection) and HDL-cholesterol levels on commencing antiretroviral treatment.

Treated HIV patients with undetectable HIV viral loads were followed every 3 months for 36 months. The authors measured total cholesterol, HDL cholesterol, triglycerides, previous responses to antiretroviral treatment, opportunistic infections, sex and age.These variables were assessed in relation to the time of undetectable viral load until viral rebound. Amino acid sequence alignment was performed with HIV proteins and apolipoprotein A1 to detect shared similarity.

The Cox proportional hazards model showed a significant association between HDL cholesterol and the time of undetectable viral load.The other variables studied were not associated.There was 30% sequence similarity in an area of 50 amino acids shared between apolipoprotein A1 and p17 Gag-HIV protein.

High levels of HDL cholesterol are associated with a better viral response in treated HIV patients. This association could be related to the sequence similarity and structure homology between apolipoprotein A1 and p17 Gag-HIV protein, which raises the intriguing clinical possibility that inducing an increase in HDL could assist HIV therapy.

(Alonso-Villaverdea C, *et al. AIDS* 2003; **17**(8):1173-1178.)

A novel coronavirus associated with SARS

A worldwide outbreak of severe acute respiratory syndrome (SARS) has been associated with exposures originating from a single ill health care worker from Guangdong Province, China. Studies were conducted to identify the aetiological agent of this outbreak.

The authors received clinical specimens from patients in seven countries and tested them, using virus isolation techniques, electron-microscopical and histological studies, and molecular and serological assays, in an attempt to identify a wide range of potential pathogens.

None of the previously described respiratory pathogens were consistently identified. However, a novel coronavirus was isolated from patients who met the case definition of SARS. Cytopathological features were noted in Vero E6 cells inoculated with a throat-swab specimen. Electron-microscopical examination revealed ultrastructural features characteristic of coronaviruses. Immunohistochemical and immunofluorescence staining revealed reactivity with group I coronavirus polyclonal antibodies. Consensus coronavirus primers designed to amplify a fragment of the polymerase gene by reverse transcription-polymerase chain reaction (RT-PCR) were used to obtain a sequence that clearly identified the isolate as a unique coronavirus only distantly related to previously sequenced coronaviruses. With specific diagnostic RT-PCR primers several identical nucleotide sequences were identified in 12 patients from several locations, a finding consistent with a point-source outbreak. Indirect fluorescence antibody tests and enzyme-linked immunosorbent assays made with the new isolate have been used to demonstrate a virus-specific serological response.This virus may never before have circulated in the USA population.

A novel coronavirus is associated with this outbreak, and the evidence indicates that this virus has an aetiological role in SARS. Because of the death of Dr Carlo Urbani, the authors propose that this first isolate be named the Urbani strain of SARS-associated coronavirus.

(Ksiazek G *et al. NEJM* 2003; **438:** 1953-1966.)