Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Encouraging adoption of new children's vaccines through the development of methods for decision support modelling

1. Summary of the impact

LSHTM researchers have developed four computer models to help decision-makers make evidence-based choices about new vaccines and vaccine schedules. These models analyse the public health impact and cost-effectiveness of different options under different assumptions and scenarios on a country-by-country basis. They are used by national immunisation managers and key decision-makers, international committees and partner organisations (e.g. the Global Alliance for Vaccines and Immunisation and the Bill & Melinda Gates Foundation). LSHTM's researchers have built on this research for WHO, informing global recommendations on vaccine timing and schedules.

2. Underpinning research

An estimated 1.5m children in low/middle income countries die every year from vaccine-preventable diseases such as diarrhoea and pneumonia. New vaccines are among the most effective health interventions ever developed, but can also be costly. The development of tools to assist policy-makers in weighing the impact of a vaccine against cost and other related factors has been the focus of research led by Colin Sanderson, Professor of Operational Research in Health Care (at LSHTM since 1981, then Lecturer) and Andrew Clark, Research Fellow (LSHTM, 2002–).

In 2007, Sanderson and Clark began developing TRIVAC, a decision-support model that calculates the impact and cost effectiveness ratios for childhood vaccines against *Haemophilus influenzae* type b (Hib), pneumococcus and rotavirus (RV).[3.1] Parameters such as demography, disease burden, vaccine costs, coverage, efficacy, health service utilisation and costs, as well as data from international sources (e.g. WHO and Centers for Disease Control and Prevention – CDC) were assembled and loaded into the model. Data from published literature were also used. The aim was to allow national policy-makers to estimate the benefits of each new vaccine in terms of mortality, morbidity and disability adjusted life-years (DALYs) based on national estimates of disease burden and of vaccine coverage and timeliness, and regional estimates of vaccine efficacy. Most of this work was done as part of the Pan-American Health Organization's (PAHO) ProVac project, and TRIVAC was launched at ProVac workshops in South and Central America in 2008.

Clark also developed the CERVIVAC model in 2011 using a similar interface to TRIVAC to evaluate the impact and cost effectiveness of human papilloma virus (HPV) vaccine – used to help protect against cervical cancer. This incorporates results from the model developed by Susan Goldie's group at Harvard to allow for different cervical cancer screening scenarios.

Between 2008 and 2012, LSHTM researchers developed a risk/benefit model for rotavirus to conduct scenario analyses assessing the potential benefits of mortality reduction from rotavirus versus the risk of fatal intussusception when the first dose of vaccine has to be administered by 15 weeks of age, compared with 1 year of age. They concluded that in developing countries, the additional lives saved by broadening the age restrictions for initiation of rotavirus vaccination would far outnumber the hypothetical excess intussusception deaths that might accompany such an approach.[3.2]

The schedules model was developed (2012–2013) to help evaluate the public health impact of alternative Hib vaccine schedules. For this purpose LSHTM researchers have re-analysed existing national and regional data about the distribution of deaths among children from diseases that are preventable by vaccination, and actual ages at each vaccine dose. Additional research by Sanderson and Clark has involved assembling other data necessary for these models, including a review of literature on the prevalence of disabling sequelae after bacterial meningitis,[3.3] analysis of vaccination coverage at different ages in 45 low- and middle-income countries,[3.4] and reviews of

data to determine variations in vaccine efficacy measured against number of doses and region.[3.5]

3. References to the research

3.1 Clark, A, Jauregui, B, Griffiths, U, Janusz, C, Bolaños-Sierra, B, Hajjeh, R, Andrus, JK and Sanderson C (2013) TRIVAC decision-support model for evaluating the cost-effectiveness of *Haemophilus influenzae* type b, pneumococcal and rotavirus vaccination, *Vaccine*, 31(Suppl. 3): C19–C29, doi:10.1016/j.vaccine.2013.05.045.

3.2 Patel, MM, Clark, AD, Sanderson, CFB, Tate, J and Parashar, UD (2012) Removing the age restrictions for rotavirus vaccination: a benefit-risk modeling analysis, *PloS Medicine*, 9(10): e1001330, doi:10.1371/journal.pmed.1001330.

3.3 Edmond, K, Clark, A, Korczak, VS, Sanderson, C, Griffiths, UK and Rudan I (2010) Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis, *Lancet Infectious Diseases*, 10(5): 317–328, doi:10.1016/S1473-3099(10)70048-7.

3.4 Clark, A and Sanderson, C (2009) Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data, *Lancet*, 373(9674): 1543–1549, doi: 10.1016/S0140-6736(09)60317-2.

3.5 Griffiths, UK, Clark, A, Gessner, B, Miners, A, Sanderson, C, Sedyaningsih, ER and Mulholland, KE (2012) Dose-specific efficacy of *Haemophilus influenzae* type b conjugate vaccines: a systematic review and meta-analysis of controlled clinical trials, *Epidemiology & Infection*, 140(8): 1343–1355, doi:10.1017/S0950268812000957.

Key grants

Clark, Evaluation of introducing Rotovirus & Pneumococcal Vaccines, PAHO, 1/10/2012–31/12/2014, £113,207.
Sanderson, OLIVES (Extension), PAHO/WHO, 1/07/2009–31/12/2014, £328,722.
Sanderson and Clark, Project Proposal to Transfer Tools, Methods and Lessons (ProVac), Bill & Melinda Gates Foundation, 4/07/2012–31/12/2013, £115,714.

4. Details of the impact

LSHTM models measuring the cost effectiveness and impact of new vaccines are now being used by key stakeholders and vaccine policy-makers at national and international levels to provide evidence for and support health initiative decisions. The models have been used by country teams including experts from Ministries of Health and Finance, and national vaccination programme managers. In 10 of these countries the new vaccine in question has been introduced, benefiting many thousands of children. Sanderson and Clark have also been regularly called upon to provide analysis and advice for policy-makers, donors and stakeholders at the highest level.

TRIVAC and CERVIVAC

Launched in 2010, TRIVAC is now an integral part of international efforts to collect and disseminate data and research to help countries build or scrutinise the case for adopting vaccines. TRIVAC has been used to expedite national decision-making around Hib vaccination in the developing world (through GAVI's 'Hib Initiative') [5.1] and to support country-level evidence-based decisions about adopting new vaccines in countries who are members of the PAHO through its ProVac Initiative.[5.2] It has also been used by the GAVI Alliance (a public-private health partnership aimed at increasing international access to immunisation).

Between 2010 and July 2013, TRIVAC and/or CERVIVAC were used in 14 vaccine cost effectiveness studies in the PAHO region. Typically, this has followed an invitation from national policy-makers to conduct workshops for teams made up of local Ministry of Health and immunisation officials, during which an LSHTM researcher (usually Clark) uses the model(s) to scrutinise data, consider plausible scenarios and carry out sensitivity analyses.

Following these studies, a pneumococcal conjugate vaccine (PCV) has been introduced in

Argentina, Bolivia, Costa Rica, Ecuador, El Salvador, Nicaragua, Paraguay, Peru and Guatemala. Guatemala has also introduced a rotavirus vaccine. CERVIVAC was launched in 2011, and a study using this model was reviewed prior to HPV vaccination being introduced in Argentina. Decisions are pending following studies in Bolivia, Ecuador and Jamaica.[5.3]

In October 2012, a TRIVAC analysis by the Costa Rican Department of Social Security restored public confidence in PCV for children under the age of 2, after a controversially expensive universal vaccination programme was introduced.[5.4]

In 2009/2010 TRIVAC was used by Sanderson in a World Bank/GAVI study of cost-effectiveness and financial consequences of new vaccine introduction in Pakistan.[5.5] Since 2010 TRIVAC has also been used by WHO to generate annual immunisation progress reports for GAVI.[5.5] These reports include estimates of deaths prevented by new vaccines in the world's 70 poorest countries, and estimates of the health benefits attributable to GAVI-financed vaccines.

Seven further TRIVAC cost-effectiveness analyses are currently (7/2013) in progress in Albania, Azerbaijan, Croatia, Egypt, Georgia, Iran and Senegal.

The rotavirus risk/benefit model

In April 2012 Sanderson presented the results of the LSHTM rotavirus study at a meeting of WHO's Strategic Advisory Group of Experts (SAGE) on immunisation. LSHTM evidence regarding the additional lives saved by changing the age restrictions for initiation of the rotavirus vaccination resulted in their review. Further LSHTM findings were presented in a follow-up meeting which resulted in SAGE issuing that same year a new recommendation to relax age restrictions for rotavirus vaccination. LSHTM findings are quoted as evidence in related WHO documents.[5.6, 5.7]

The schedules model

Results for Hib from the schedules model were presented by Clark and Sanderson to SAGE at meetings in October and November 2012 and April 2013. Drawing on this evidence, at the April meeting SAGE recommended two possible schedules countries should choose between dependent on local epidemiology and health system considerations. SAGE also recommended use of the schedules model to help countries with this task,[5.8] and Clark and Sanderson have developed a website for WHO that carries relevant country-level data and analyses (www.vaccine-schedules.com).

Making research findings available to policy-makers and other users

In 2012, supported by PAHO and WHO, LSHTM launched a new website 'OLIVES' (On-line International Vaccine Economics and Statistics) which provides access to new analyses of data from LSHTM, new data and literature reviews from universities in the PAHO region, including details and quality assessments of studies reviewed, and relevant extracts from international databases.[5.9] Designed to be used by policy-makers and analysts to provide financial and health benefit evidence and support for vaccine decisions, the site is regularly updated and provides an accessible reference source for information on vaccine economics and statistics, for use in conjunction with LSHTM models or otherwise.

5. Sources to corroborate the impact

5.1 Director, Division of Bacterial Diseases, Center for Disease Control, Atlanta Georgia, USA.

5.2 Jauregui, B, Sinha, A, Clark, AD, Bolanos, BM, Resch, S, Toscano, CM, Matus, CR and Andrus JK (2011) Strengthening the technical capacity at country-level to make informed policy decisions on new vaccine introduction: lessons learned by PAHO's ProVac Initiative, *Vaccine*, 29(5): 1099–1106, doi:10.1016/j.vaccine.2010.11.075, http://www.sciencedirect.com/science/article/pii/S0264410X10017196 (accessed 12 September 2013) (see p. 1101 panel 1 and section 3.1, for example).

5.3 Project Manager, ProVac Initiative, PAHO.

5.4 Fallas, CV (2012) Vacuna contra neumococo ahorrará casi $24 millones al Seguro Social, *Al Dia* (Costa Rica) (Spanish), 13 October 2012, http://www.aldia.cr/ad_ee/2012/octubre/13/nacionales3352605.html (accessed 3 October 2013).

5.5 Manager, Strategic Information Team, Expanded Programme on Immunization (EPI), Initiative for Vaccine Research, WHO.

5.6 Team Leader, Implementation Research and Economic Analysis, Initiative for Vaccine Research, Department of Immunisation Vaccines and Biologicals, WHO.

5.7 WHO (2013) Rotavirus vaccines: WHO position paper January 2013', *WHO Weekly Epidemiological Record*, 88(5): 49–64, http://www.who.int/wer/2013/wer8805.pdf (accessed 12 September 2013) (references to LSHTM work in footnotes 2 and 23).

5.8 WHO (2013) Meeting of the Strategic Advisory Group of Experts on immunization, April 2013: conclusions and recommendations, *WHO Weekly Epidemiological Record*, 88(20): 201–216, http://www.who.int/wer/2013/wer8820.pdf (accessed 12 September 2013) (LSHTM mentioned on p. 14).

5.9 http://provac-olives.com/ OLIVES website. (accessed 21 November 2013)