Recent developments in immunisation practice

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Abstract

Over the last 5 years the UK has led the world in the introduction of new vaccines with substantial changes in the childhood vaccination schedules. These have been both in response and in anticipation of changes in the epidemiology of illness and demonstrate the importance of public health screening and the notification of infectious diseases. This review article briefly outlines the rationale and history behind these most recent developments and highlights potential changes on the horizon.

Keywords influenza; meningococcus; pertussis; rotavirus; vaccines

Rotavirus

Epidemiology

Rotavirus (RV) is the single most important cause of infectious diarrhoea in young children worldwide and is responsible for almost half a million deaths every year. Mortality related to RV infections is almost exclusively in resource-poor countries. In wealthier societies without high uptake vaccine programmes the infection remains common and the accompanying morbidity results in much distress and suffering as well as significant healthcare and societal pressures and costs. In temperate regions, RV infection occurs as annual epidemics usually peaking in early spring. Almost all children will have encountered the disease at least once by the age of five and the majority before the age of two. The virus is transmitted via the faeco-oral route and is abundantly excreted in stool during and sometimes for several weeks after the resolution of clinical symptoms. As few as ten viral particles are sufficient to cause clinical disease in susceptible individuals, which makes reliable prevention of spread of the infection by hygiene measures effectively impossible.

Vaccines for rotavirus

The early history of RV vaccines had a profound effect on their subsequent development and uptake. In the 1990s the first licensed oral RV vaccine (RotaShield® Wyeth) completed phase III trials and rapidly went into use in the USA. However after 9 months post-marketing surveillance suggested clustering in incidence of intussusception (IS) particularly in the period following the first dose in vaccinated individuals, leading to the voluntary withdrawal of the vaccine from the market. Nearly 10 years later in 2006, two new live oral vaccines were licensed in Europe, Rotarix (GlaxoSmithKline Biologicals) and RotaTeq (Merck & Co., Sanofi Pasteur-MSD).

Rotarix is a monovalent attenuated human RV strain given to infants of 6–24 weeks of age as two oral doses at least 4 weeks apart. Phase III trial in more than 63,000 children reported no increase in rates of IS, 85% effectiveness against hospital admissions, 85% against severe disease and up to 100% against very severe disease. An efficacy trial carried out in South Africa and Malawi reported 61.2% efficacy against severe disease and although it was lower in the more resource-poor Malawi (49.4% vs South Africa 76.9%), the impact on mortality was predicted to be higher due to higher burden of disease there.

RotaTeq is a pentavalent vaccine combining human–bovine reassortant strains and is given to infants 6–33 weeks of age as three oral doses at least 4 weeks apart. Pre-licensure studies in more than 69,000 children also showed no increase in rates of IS, 74% protection against all RV gastroenteritis and 98% protection against severe disease with an almost 95% reduction in emergency room attendance and 86% reduction in missed work days by parents of vaccinated children. Large efficacy trials in Asia and sub-Saharan Africa found 48.3% and 39.3%, respectively protection against severe disease. The consistent finding of reduced efficacy in countries with lower socio-economic status is still not clearly understood and is likely to be multi-factorial. Proposed contributing factors are higher rates of breastfeeding (containing higher titres of anti-rotavirus antibodies), oral polio vaccine use, higher prevalence of other viral and bacterial gut infections, malnutrition and other socio-economic factors. Nevertheless because of high RV mortality rates in these countries, it is here that the vaccines have the potential to prevent hundreds of thousands of diarrhoea-related deaths.

Approaches to roll out

In 2009 the World Health Organization (WHO) — Strategic Advisory Group of Experts (SAGE) recommended that RV vaccine be introduced to all countries' immunisation programmes. But the decision to implement this advice is influenced by each

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country's healthcare system and burden of disease. In regions such as Western Europe that have low rates of mortality, inclusion has been gradual with only seven countries currently giving RV vaccine routinely, although in most of the other countries the vaccines are also available privately – usually resulting in limited coverage and so few herd effects. Almost all mortality due to RV occurs in the very poorest countries and the Global Alliance on Vaccines and Immunisation (GAVI) was set up with the aim of meeting the Millennium Development Goal 4 – reduction in childhood mortality. They have pledged to give financial support to help introduce childhood vaccines in a sustainable way, pooling demand to shape vaccine markets and helping fund vaccines through a co-payment process. By supporting the upfront cost of vaccine introduction, the hope is that resulting socio-economic and healthcare savings will facilitate ongoing use. GAVI has been able to secure RV vaccines at $5 per course compared to around $45 per dose in the open market. Eligible countries can then obtain them from GAVI for just $0.20 per dose. Of the 81 countries now including rotavirus vaccines in their routine schedule (Figure 1), 31 are supported by GAVI.

Intussusception following RV immunisation

Although both the large pre-licensure trials did not detect any increase in rates of IS, since the two current vaccines were introduced to widespread clinical use, national surveillance data from Australia, Mexico, Brazil and the USA have shown convincing evidence of an association for both of them at a rate of around 1 in 50–100,000. It remains unclear whether these represent additional cases or precipitation of cases that would otherwise have occurred later. The current position of the WHO Global Advisory Committee on Vaccine Safety (GACVS) is that "based on available evidence, the benefits of RV vaccination to all infants, without age restriction, would greatly exceed the risks, particularly in developing countries with moderate and high mortality from RV disease".

Implementation and impact of RV immunisation programmes

The UK introduced Rotarix into the routine childhood schedule in July 2013 and rapidly achieved 98% first dose coverage. The first season after introduction saw estimated reductions of up to 150,000 general practice attendances, 35,700 ED attendances and 8120 admissions to hospital. A population case–control study identified an increased risk of intussusception in the 1–7 days after vaccination with an estimated additional 21 cases following vaccination, all of whom were treated successfully. Experience in similar high income countries such as the USA, Australia, Israel, Belgium, Austria, Luxembourg and Finland which have introduced routine RV vaccination shows it to be highly effective (90% prevention of hospital admission) and to result in large reductions in healthcare costs. In middle and lower income countries it has been shown to have profound effects on childhood mortality. In Mexico a 46% reduction in under five mortality due to gastroenteritis has been shown. Early post-implementation data from the GAVI countries are also positive with reports of reductions in rates of hospitalisation by 50% and vaccine effectiveness estimated at 65%.

There are many low cost high volume alternative vaccines at varying stages of development. Notably India has developed its own, costing $1 per dose. Injectable inactivated vaccines are also in very early development and with proposed benefits such as increased heat stability, lack of association with IS and less vulnerability to environmental interference, they may ultimately prove to be an effective alternative approach.

With the current vaccines now having been in use for 10 years and with many millions of doses given, no new problems with serious side effects or strain switching have materialised to date. In high income settings significant economic savings have been seen consistently whereas in low resource settings there have been significant reductions in mortality. With so many countries of the world now sparing their children from this disease, it will be of interest to observe how long it takes the rest to follow suit and introduce universal infant vaccination against RV.

Meningococcus

Epidemiology

Despite a substantial reduction in annual laboratory-confirmed cases of invasive meningococcal disease (IMD) in the UK over the past 15 years (2448 in 2000–2001 to 805 in 2015–2016,

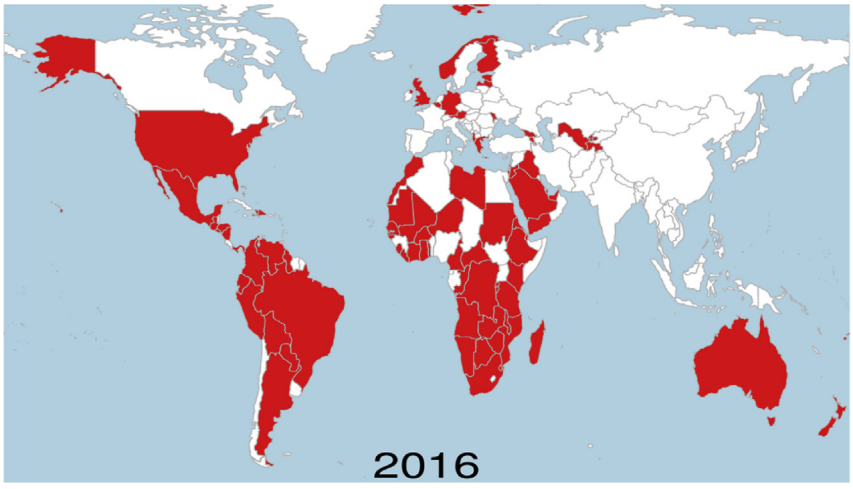

Figure 1 Current worldwide use of RV vaccine. (Data used with permission from World Health Organization http://www.who.int/entity/immunization/monitoring_surveillance/data/year_vaccine_introduction.xls?ua=1 accessed 06/2016).