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ANALYSIS

Do we need a new approach to making vaccine recommendations?

Controversy about the evidence, economics, ethics, lobbying, and decision making surrounding a new vaccine for serogroup B meningococcal disease should trigger change in the way we develop recommendations for new vaccines say **Natasha Crowcroft and colleagues**

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We are on a steep trajectory away from an era of inexpensive vaccines for diseases that are widespread in the absence of immunisation. Vaccines are increasingly being produced for diseases that are devastating at an individual level but have less impact on population health. Moreover, the costs of developing and getting a vaccine to market are rising because of increasingly complex technologies and the public intolerance of adverse events. For these reasons new vaccines are likely to be less cost effective than older vaccines and are unlikely to be cost saving (fig 1⇓).[1]

Technologies such as searching genetic codes for possible antigens and the development of new adjuvants to stimulate immune responses also bring considerable uncertainty about safety and effectiveness.[2] It may take many years for adverse events caused by vaccines to be identified and confirmed, as was the case for the link between a pandemic H1N1 influenza vaccine (plus adjuvant) and narcolepsy.[3 4]

These challenges come at a time when some sections of society are less likely to vaccinate themselves or their children. Those who hesitate to vaccinate are often highly educated, well resourced, and demand respect for their perspectives.[5] How best to reassure the public is unclear. But all the components of decision making about vaccination programmes must be high quality and transparent and should stand up to external scrutiny to sustain the confidence of both the public and healthcare providers.[6-8]

To illustrate the tensions related to making the decision to publicly fund new vaccines, we discuss a vaccine for serogroup B meningococcal disease, Bexsero (Novartis, Basel) (box).

A novel vaccine

Bexsero was approved by regulatory agencies in 2013, first in Europe in January, then in Australia in August and Canada in December.[9-11] The multi-component vaccine includes three protein antigens that were identified through reverse vaccinology. This technique had never been used for vaccines before—it involves sequencing the whole bacterial genome and using bioinformatics to identify sections that seem to code for important antigens on the outer membrane of the bacterium. Bexsero is expected to be the first of many such vaccines. It is currently not included in any national vaccination programmes.

Advisory committees consider evidence

Vaccines follow a structured process from research to implementation (fig 2⇓). Most countries have national immunisation technical advisory groups to help governments make decisions about the public funding of vaccines. The first such group to consider Bexsero was the Joint Committee on Vaccines and Immunisation (JCVI) in the United Kingdom. It responded in July 2013 with an interim position statement, which concluded that it did not support use of the vaccine in a publicly funded programme based on the likely lack of cost effectiveness.[12] This triggered considerable reaction in the medical literature and pressure from groups advocating on behalf of those affected by serogroup B invasive meningococcal disease, including clinicians, meningitis charities, and the vaccine manufacturer.[13-19]

The committee responded in March 2014 with a follow-up statement and a revised recommendation that the vaccine should be used if a cost effective price could be negotiated.[20] Then in April the health secretary for England, Jeremy Hunt, asked the company to bring the price down to a level that the country could afford.[21]

Major challenges to making a decision in favour of the vaccine were uncertainties about safety, effectiveness, duration of protection for individuals and for populations (herd immunity), the burden of disease in terms of incidence and long term effects, the proportion of strains against which the new vaccine would

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Key facts about meningitis B vaccine Bexsero

- First vaccine for serogroup B meningococcal disease intended for mass population use
- First vaccine developed using antigen mining and reverse vaccinology; three quarters of the protective antigens are novel
- First vaccine that may have effectiveness across multiple serogroups and clonal complexes and that includes antigens found in other *Neisseria* species
- First vaccine to be widely marketed in multiple jurisdictions before clinical effectiveness data were available
- Uncertainty about its effectiveness and its capacity to interrupt circulation of the bacteria and sustain herd immunity
- Worse safety profile than meningococcal vaccines currently publicly funded in mass programmes

protect, and the number of doses required to achieve all of the above. Such uncertainties require expert judgment, and the decisions will affect the results of health economic modelling—the same data could be interpreted differently by different groups, and the results could vary if experts changed their advice.

By framing the problem as one of pricing, the government transferred responsibility to the drug industry and avoided being held responsible for denying the vaccine to children. This distracted from other elements underpinning the recommendation, including how ethics, transparency, uncertainty about the efficacy and evidence, and explicit discussion of the opportunity cost were factored into decision making.

The health economic modelling used by the JCVI for its original decision was modified at the request of the committee itself, and the new analysis found that the vaccine would be cost effective at a low price.[22 23] Details of the modified economic analyses and decision making were not available at the time, but two studies have since been published.[24 25] The modified analysis included the costs of litigation to the health service arising from safety problems or other unforeseen hazards.[10] We don't know what the price of the vaccine for a national programme would be. But even at £10 (€13; $15) per dose, a birth cohort of 600 000, and the need for four doses, the cost of the vaccine would be £24m a year, without the additional costs of, for example, delivery.

Other vaccines have been included in the vaccination schedule without evidence of effectiveness. The UK introduced the vaccine for group C meningococcal disease in the absence of data on its effectiveness. However, differences in the epidemiology of group C and B disease and their vaccines make this precedent less relevant. The incidence of group C disease was increasing when the vaccine was introduced into the UK, whereas that of group B is falling. The antigen used in the group C vaccine is established and other vaccines of its type (conjugate vaccines) are effective in generating herd immunity and preventing *Haemophilus influenzae* type b disease. By contrast, there are no data to show that the antigens in the meningitis B vaccine are protective in vivo or will lead to herd immunity. Evidence exists that some of its antigens are differentially up-regulated or down-regulated depending on whether the organism is in the laboratory, the throat, or the bloodstream, which may affect their ability to protect against disease.[26]

Economics and ethical considerations

Most countries have similar committees to the UK, but they don't all consider the economics of vaccine implementation. No other country has recommended a publicly funded vaccination programme for group B meningococcal disease, and several countries have made negative recommendations, including Canada (where the national advisory committee does not normally consider economics) and Spain.

Vaccination programmes are generally funded from siloed national health budgets. To make better decisions about which vaccines to fund, and to enable transparency about potential losses as well as gains, options need to be placed in the context of all healthcare, not just compared with other vaccines. To aid the analysis of potential vaccine programmes Erickson and colleagues developed an analytical framework.[27] We have used their framework to assess Bexsero (table⇓).

Evidence, economics, and ethics are three key pillars of policy making. One element should not trump the others, but ethical concerns are often relegated to a subordinate role.[27] Health economics cannot sanitise difficult decisions. Moreover, complex economic modelling may obfuscate the ethical values that are intrinsic to decision making. For example, the backlash against the UK decision on Bexsero was not about money; it was about the priority placed on child health and the emotional impact of a life changing illness.

Any public vaccination programme for group B meningococcal disease will have unintended effects. The vaccine schedule for infants is already so full that parents and healthcare professionals are objecting to giving further vaccines at any single visit.[28] Adding vaccines to the schedule may cause parents or clinicians to choose between vaccines—for example, delaying or forgoing DTP vaccine because meningitis is perceived to be more dangerous. If the new vaccine were associated with adverse events after the programme was extended to the larger population, public acceptability of other routine vaccines could be adversely affected.

The ethical dimensions of decision making by national advisory committees and governments could be made explicit and integral to the assessment of evidence and health economic analyses. Inclusion of an ethicist on the committees may help. The articulation of an explicit ethical framework has aided diverse stakeholders in negotiating complex ethical matters in others areas of healthcare, such as pandemic preparedness.[29] Such frameworks outline principles related to the overarching goals of the decision, often including concerns for justice, equity, and non-discrimination, as well as procedural elements of transparent, fair, and inclusive decision making. All of these should be explicitly noted and agreed on.

Competing interests

Lobbying may have influenced the alteration of the JCVI decision. It is no surprise that paediatricians and relatives of patients who have had invasive meningococcal disease have been vocal in their support of the vaccine. They may have understandable bias, influencing how they view vaccine policy. Some vocal clinicians also have strong links with the drug industry, and this has not been evident in the public discourse. Debate about the vaccine is difficult when respected physicians state that the vaccine works without declaring their industry funding.[30] We risk losing public trust and supporting baseless anti-vaccination sentiment by allowing drug manufacturers or

people with close links to industry to be involved in decision making and lobbying.[6]

The expert committee that advised the UK government about Bexsero could not participate in a public conversation at the time because its advice had to be approved before release. The minutes from the meeting posted on the Department of Health website are not detailed enough to capture all the parameters of health economic modelling required to understand the conclusions. Perhaps then, it is not surprising that conspiracy theories emerged, including the idea of undue influence of industry on the decision.[31]

International framework

The controversy surrounding Bexsero should trigger fundamental changes in the way we develop recommendations on new vaccines. Many tensions need to be balanced in this process—individual against population benefit, clinicians against public health professionals, governments against industry, and advocates for children against other members of society (fig 3⇓).

Technical and economic considerations currently dominate ethical ones. It is time for the ethical dimensions of decision making by national advisory committees and governments to be made explicit and integral to assessing evidence and health economic analyses. We call for an internationally agreed framework that provides clarity about what may be lost as well as gained when making decisions, communicates uncertainty effectively, makes conflicts of interest more transparent, and engages the public in balancing ethical considerations, health economics, and the public health impact of new vaccines.

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Table

Table Table| Applying the Erickson et al framework[27] to the meningitis B vaccine Bexsero

Framework element	Bexsero
1. Burden of disease	Low
2a. Vaccine efficacy	Efficacy unknown; impact on nasal carriage unknown; immunogenicity data supportive; MATS testing not available to Canadian public health authorities
2b. Vaccine safety	Safety concerns raised, including fever
3. Immunisation strategy (ie, suitability for outbreaks or high risk populations)	Under consideration
4. Cost effectiveness	Not cost effective in most analyses published
5. Acceptability	Highly acceptable to the population
6. Feasibility	Feasible, but risk that coverage of other vaccines may be affected by adding to vaccination schedule
7. Ability to evaluate programme	Challenging without implementing it
8. Research questions	Considerable uncertainty about effectiveness
9. Equity	Can be purchased privately, leading to inequity in absence of public funding
10. Ethical considerations	When health spending is limited, the decision to purchase this vaccine denies the opportunity to prevent other causes of mortality and morbidity (opportunity cost), including those that are preventable with vaccines, but these are not considered
11. Legal considerations	Doctors may be legally obliged by their professional bodies or insurers to recommend the vaccine to parents whether or not it is funded
12. Conformity of programmes	If made available to a subgroup, pressure to make it available elsewhere may increase. Unlikely to be an increased absolute risk of disease to other populations from a targeted programme
13. Political considerations	Lobbying is likely as it has the potential to prevent a severe and much feared disease of children

MATS=meningococcal antigen typing system.

Figures

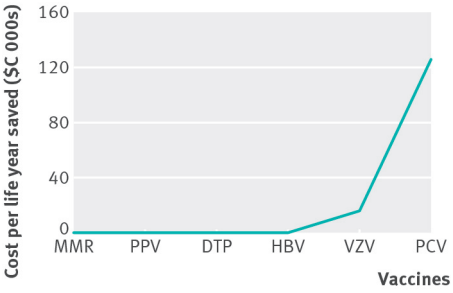

Fig 1 Newer vaccines cost more per life year saved than older vaccines. Currency: $C1; £0.5; €0.7; $0.8. DTP=diphtheria, tetanus, pertussis vaccine, HBV=hepatitis B virus screening and immunisation of newborns, MMR=measles, mumps, and rubella vaccine, PCV=pneumococcal conjugate vaccination for children, PPV=pneumococcal polysaccharide vaccine, VZV=varicella zoster vaccine. Source: Canadian Immunisation Guide.[1]

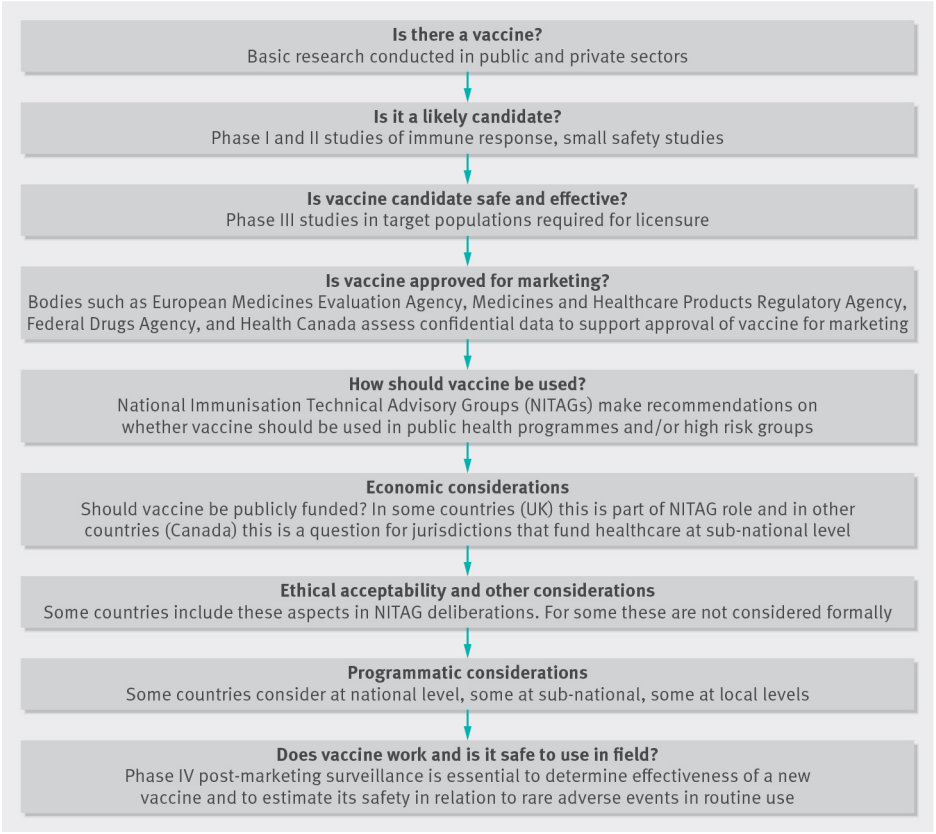

Fig 2 Vaccine development—from invention to inclusion in a public programme

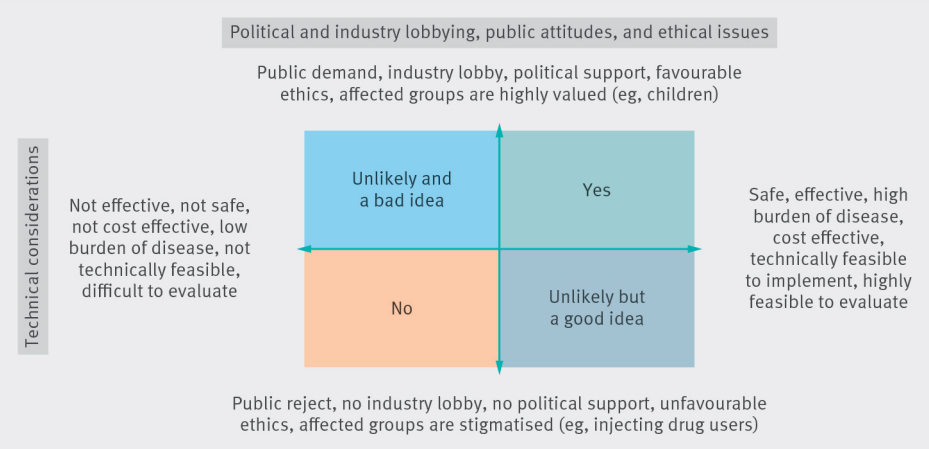

Fig 3 Influences on a decision to publicly fund vaccines