Review of Cost-Effectiveness Methodology for Immunisation Programmes & Procurements

(CEMIPP)

Report presented to the Department of Health

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Introduction

1. - Around the time that Cost-Effectiveness Methodology for Immunisation Programmes and Procurements (CEMIPP) working group was being planned the Department of Health (DH) initiated an Appraisal Alignment Working Group (AAWG), first meeting 5th March 2014, with Keith Derbyshire (Chief Economist, DH) as chair. The purpose of the AAWG is to characterise the range of practice across organisations, to understand the reasons for divergence in practice, to consider the possibility of identifying "best practice" where possible, and to make proposals, where appropriate, for measures to align practice.

2. - The likelihood that the AAWG will produce advice regarding best practice which the JCVI (and other decision making bodies) might be expected to follow unless there are compelling reasons or Ministers decide to do otherwise has given a sharper focus to the activities of CEMIPP. In short, CEMIPP addresses the question whether there are ways in which the economic evaluation of immunisation programmes differs sufficiently from that of other health-related activities using public resources such that it would be appropriate for the methods for appraising cost-effectiveness to differ in specific ways from those proposed by the AAWG.

3. - While the title of the working group explicitly includes "procurements", the terms of reference were "To consider all aspects of the determination of the cost-effectiveness of a proposed or existing immunisation programme based on appropriate epidemiological analysis and modelling". The working group only considered procurement to the extent that current procurement practice had implications for the determination of cost-effectiveness. Accordingly, the working group has not made any specific recommendations with respect to procurement.

Mode of working

4. - The working group first met on 15th September 2014 and decided to tackle its remit by setting up three sub-groups. These were led by Professor Martin Utley, Professor Steve Morris and Professor Stavros Petrou and drew their membership primarily from CEMIPP but invited the participation of others where appropriate. The ongoing deliberations of the sub-groups were discussed at full meetings of CEMIPP. At the thirteenth meeting of CEMIPP (22nd January 2016) a draft report based on individual sub-group reports was presented by the chair.

Recommendations

5. - The recommendations are grouped under seven headings: perspective, incremental analysis, discounting, time horizon, cost-output relationship, valuation of health effects, and appraisal of evidence. While these recommendations are not independent

and should be viewed as a package it is recognised that the DH have discretion over which recommendations should or should not be adopted.

Next steps

6. - The next steps are primarily the responsibility of others – with the production of this report the working group will have met its remit. The DH may wish to hold a consultation with stakeholders regarding the working group's recommendations. It is anticipated that JCVI along with other arms-length bodies will be asked to respond to the on-going work of AAWG to codify best practice appraisal methods. It is to be hoped that this report will provide a robust starting point for such a response. It might be advantageous if some members of the CEMIPP working group were to assist JCVI with their response. For other stakeholders it is hoped that this document at least brings greater clarity to how JCVI can or should appraise immunisation programmes.

Section 1: Perspective on costs and outcomes

7. - There are several issues to consider regarding the perspective to be adopted with respect to costs and outcomes. First, should decisions on the introduction of immunisation programmes and on the procurement of vaccines be based on maximising the net health benefit of the programme (i.e. QALYs gained from the programme minus the QALYs forgone by displacing other treatments) or is it more appropriate to base decisions on an assessment of all the costs and benefits regardless of their source? Second, if decisions are primarily concerned with net health benefit (rather than full economic utility) would it be appropriate in some circumstances to include a subset of wider factors? Third, should QALY losses to family members and carers ever, sometimes or always be included in evaluations?

8. - Our understanding is that the position likely to be taken by the AAWG is that, unless the remit of an evaluating body dictates otherwise, evaluations would ideally encompass all impacts on people, which is interpreted as being the full economic utility. The word "ideally" is important here as the AAWG are currently considering issues of proportionality and materiality – a complete cost benefit analysis of all impacts on all people is resource intensive and the additional costs may not be justified.

9. - Whether immunisation is a special case with respect to the impacts that should be included in evaluations can be approached from three perspectives: (1) that of JCVI as a decision making body, (2) that of immunisation as a mode of intervention, and (3) that of vaccine preventable diseases as a group of conditions.

    a) - The remit of the JCVI includes "To advise UK health departments on immunisations for the prevention of infections and/or disease following due consideration of the evidence on the burden of disease, on vaccine safety and efficacy and *on the impact and cost effectiveness* of immunisation strategies." This remit does not specifically limit the impacts to be considered in evaluations to health impacts and so consistency with AAWG on this point would suggest that subject to proportionality and materiality considerations, evaluations of immunisation programmes should encompass full economic utility.

    b) None of the issues regarding perspective outlined above concerning the - scope of evaluations relate to immunisation *as a mode of intervention*. -

    c) The main area of debate concerns whether or not vaccine preventable - diseases are or should constitute a special case

10. - One argument is that vaccines confer benefits that go beyond the estimated QALYs gained and thus evaluations of vaccinations should be of sufficiently broad scope to capture these benefits. A closely related view is that there should be flexibility in the scope of evaluation on a case by case basis and potential for evaluation to incorporate the relevance of an immunisation programme to the current policy priorities of the NHS, for example, the emphasis on prevention in the NHS England Five Year Forward View.

11. - It has been suggested that, since vaccine preventable disease is often severe and often affects children, the impact can go well beyond the health of the individual (as captured by QALYs) to affect: the broader wellbeing of the individual, including educational impacts and wider life chances; the wellbeing of parents or carers; and the wellbeing of siblings. Consequently, the impacts considered in an evaluation should go beyond the health of direct beneficiaries (taken as those among whom disease is averted rather than just those immunised).

12. - It is not uncommon for those wishing to capture a wider range of impacts to stop short of supporting evaluations encompassing "full economic utility". A key concern expressed is that evaluations undertaken on the basis of full economic utility could involve the health of children being subordinated to their future economic productivity or that of their carers.

13. - Others have stressed that whatever impacts are included in evaluations of immunisation programmes, they need to be readily estimable among the displaced (the beneficiaries of activity displaced at the margin by expenditure on a new or augmented immunisation programme). Note that this concern remains given the recommendation of the working group (see below) that JCVI should continue to assess cost-effectiveness in terms of a displacement threshold.

14. - It is likely that the result of adding family and carer QALYs to evaluations would, in most cases, be to lower the threshold below which new programmes would be considered cost effective. The inclusion of wider impacts may not necessarily favour expenditure on vaccines since existing NHS expenditure also has wider impacts. Thus whether or not vaccines become more attractive will depend on whether or not the magnitude of wider impacts tends to be greater for vaccines than for other forms of health spending.

15. - Since the evaluations conducted on behalf of JCVI feed into a structured procurement process, it is not practicable for impacts other than health among direct beneficiaries to be considered unquantified on an *ad hoc* basis by JCVI.

16. - The working group considered a systematic approach developed by the Department of Health for estimating the full impact of health changes on the production and consumption of resources. The view of group members with health economic expertise was that this work has progressed to the point where it *could* be adopted as a technically defensible means of estimating the full economic impact conferred and displaced by new expenditure on immunisation programmes. Certainly it was agreed that there was not another approach available.[3]

17. - Because the approach developed shares an empirical base with the work by Claxton and colleagues on estimating the displacement threshold (that the working group recommends) adopting this approach of estimating wider impact would not be problematic, at least not from a mechanistic point of view.

[3] More detail can be found at http://onlinelibrary.wiley.com/doi/10.1002/hec.3130/suppinfo (Appendix B).

18. - While, conceptually, family and carer QALYs and non-health benefits are nested within full economic utility, this does not ensure that the current attempts at measuring full economic utility successfully encompass these benefits. Indeed, it was confirmed by Department of Health economists that the proposed approach does not, by design, capture direct effects of, say, the health of children on the health of parents and is unlikely, in practice, to capture accurately impacts on children such as educational outcomes. Use of the approach in the evaluation of immunisation would be a useful test of the extent to which it is sufficiently complete and what, if any, adjustments could be made.

Recommendations

1.1 JCVI should adopt, or trial in shadow mode, full economic utility as the scope of impacts to be assessed within evaluations if and only if this is the recommended "best practice approach" for archetypal evaluations selected by the AAWG.

1.2 Case-by-case selection (by the manufacturers, by JCVI or by modelling teams) of impacts to be considered should be avoided to promote consistency across evaluations and fairness to those whose benefits would be displaced (concerning whom bespoke analysis is intrinsically more difficult).

1.3 JCVI or DH should commission an infographic or other summary relating to the displaced benefits that can be used to inform discussions held by JCVI given the intrinsic difficulty of assessing the impact of specific factors upon the displaced.

Section 2: Incremental analysis of all relevant comparators

19. - Currently, cost-effectiveness analysis commissioned to inform a decision on whether to augment an immunisation programme targeted at a specific disease with an additional component would focus on the cost-effectiveness of the additional component and not on the cost-effectiveness of the augmented programme. We anticipate that the AAWG in its consideration of opportunity costs will also favour incremental analysis as stipulated in the Treasury guidance.

20. - An alternative view is that, so long as a programme targeted at a particular disease is cost-effective as a whole, the combination of individual components that maximises health gain should be favoured.

21. - The view among the working group tended to be that nothing about immunisation programmes warranted deviating from the principles of incremental analysis and that the key is in identifying correctly the full range of alternative programme configurations to evaluate.

22. - Similarly, the evaluation of adding a new vaccine to a product already procured was not seen as problematic from a theoretical perspective. A view was stated that, where

evaluations included assessment of current products, the DH would end up paying more than it currently does for those products. While it was accepted that evaluation might make the price DH would be *prepared* to pay increase, it was not clear that this would necessarily result in a higher price being paid.

23. - The working group considered the marginal effects of adding additional antigens to a vaccine, specifically, is it appropriate to use 'average cost-effectiveness' (total costs divided total benefits) rather than 'marginal cost-effectiveness' (marginal costs divided by marginal benefits) when considering whether or not to expand a vaccination programme to include additional antigens?

24. - Focusing on average rather than marginal cost-effectiveness is counter to the principles of economic evaluation. The focus ought to be on marginal cost-effectiveness, because otherwise buying additional QALYs for more than the incremental cost-effectiveness threshold will displace more health than it creates.

25. - Delineating and justifying the appropriate feasible options to compare in a marginal analysis is crucial, including the case of adding additional antigens to a vaccine. If for example a current vaccine with a given number of antigens will be unavailable in future then it may be appropriate to compare a new vaccine with additional antigens to 'no vaccine' rather than the current vaccine.

26. - Options to be compared in an economic evaluation should be carefully identified in advance. Sensible and plausible options should be determined by context, policy, epidemiology and other factors, as well as economic factors. The most appropriate options to be compared are likely to be identified when public health experts and economic analysts work together with JCVI and other appropriate stakeholders for a full consideration of the above factors. JCVI should be asked to advise on the clinical and scientific aspects of the options. JCVI should also continue, where appropriate, to conduct formal evaluations that include assessment of the cost-effectiveness of products already procured.

Recommendations

2.1 Evaluations of immunisation programmes should be conducted on an incremental basis.

2.2 The options to be compared should be clearly described and justified. Careful attention should be given to ensuring that the programme configurations compared comprise the range of options (including the status quo) among which the best is likely to be found, for instance including options where a new dose is added and an existing dose is removed.

2.3 JCVI should be asked to advise on the clinical and scientific aspects of the options. Public health experts should be asked to advise on practicalities of implementation and vaccine availability.

Section 3: Discounting

27. - There are three main discounting issues: what rate should be used to discount health effects, what rate should be used to discount costs, and should lower discount rates be applied to more distant events?

28. - Current practice for cost-effectiveness analysis supporting immunisation policy is to use a discount rate of 3.5% for both costs and benefits. This follows current National Institute for Health and Care Excellence (NICE) Health Technology Assessment (HTA) practice and ensures that immunisation decisions are consistent with wider NICE health technology decision making. The 3.5% figure corresponds to the default short/medium period discount rate advised in the Treasury *Green Book.* Cross government discussions have agreed that a discount rate of 1.5% should be applied to health effects (in practice QALYs). This is consistent with *Green Book* practice as it consists of only the catastrophic risk and future time preference components of the full default rate. In other words, it excludes that part of the discount rate which reflects the diminishing marginal utility of the anticipated higher levels of future consumption. This is because there is currently no agreement that future increases in health will have a declining value. Since additional expenditure from the health budget necessarily leads to an opportunity cost in terms of the health which would have been generated by the displaced expenditure, then it follows that expenditure from the health budget should also be discounted at 1.5%. Costs outside the health system and non-health benefits should be discounted at 3.5%.

29. - The working group considered that there was no reason why immunisation programmes should not be assessed under these general assumptions and that given the long term impacts of immunisation programmes the change to a 1.5% discount rate for both health costs and displaced benefits would more accurately represent the impact of an immunisation programme.

30. - The *Green Book* and DH Guidance suggest that a declining discount rate should be used for periods in excess of 30 years in the future. The working group noted that there are relatively few non-immunisation programmes for which this is a significant factor and thus it was seldom applied to analysis. For non-health programmes where 3.5% discounting was employed the difference in Net Present Value (NPV) generated by the reduction in discount rate was very unlikely to be significant. The impact of the Guidance was therefore, in practice, only of relevance to programmes such as immunisation programmes with long term costs and benefits and hence its application, in the working group's view, needed to be considered in the specific context of such programmes.

31. - The working group believes that there are a number of reasons why the application of such a declining discount rate to immunisation programmes is problematic:

a) - It removes the natural property that the impacts of the sequelae of a disease (including death) is independent of the route of calculation (i.e. the impact of the sequelae can be discounted from time of onset and then the entire impact can be discounted by time of onset).

b) - It adds practical complexity to already complicated analysis for no significant impact.

c) - At 1.5% discounting, to the extent that it does make a significant impact, applying a smaller rate in the far future exacerbates the timescale problem (discussed in the next section). Given this, the working group considers that the discount rate should not be reduced beyond the period of 30 years.

32. - In making this recommendation the working group is not (necessarily) challenging the theoretical basis of declining discount rates; rather the group notes that their use has no practical implication for the results while adding additional complexity to the calculation and potentially reducing transparency of the methodology.

33. - The working group recognises that there may be long term effects of immunisation programmes which cannot be captured by the usual discounting procedures. An example would be the eradication of a disease. The working group considered that such impacts should be specifically noted in an assessment and where possible quantified but not explicitly discounted for inclusion in the main quantitative assessment.

Recommendations

3.1 Health impacts (benefits and the displacement effects of expenditure) should be discounted at 1.5%.

3.2 Any non-health benefits and costs outside the health system, included in evaluations, should be discounted at 3.5%.

3.3 These rates should not change within the period of analysis (discussed in the next section).

3.4 Long term impacts not amenable to this discounting paradigm should be explicitly noted and assessed as part of the overall cost-effectiveness considerations.

Section 4: Time horizon of the evaluation

34. - It is generally agreed that best practice with respect to choice of time horizon is to adopt a time horizon for the evaluation that is sufficiently long to capture substantive differences in costs or effects between the intervention and the comparators. This commonly involves adopting a lifetime approach for those affected by the intervention. This lifetime perspective is sometimes pragmatically approximated by

use of a somewhat shorter time horizon justified either by relatively few differences in costs or effects arising beyond the chosen time horizon or on the grounds that the uncertainties regarding the costs and effects in the more distant future are simply too great to make a meaningful comparison.) The relevant time horizon in the case of immunisation could be a long one and this combined with the relatively low discount (recommended in section 3) creates a challenge.

35. - Immunisation programmes have effects that need to be evaluated in the long term. These can arise from complex disease dynamics (e.g. Rotavirus), 'herd' effects (e.g. meningococcal disease), long term impacts (e.g. cancer due to HPV) or long term interactions (e.g. Varicella/Zoster). In this respect immunisation programmes differ from most drug treatments and acute interventions. To capture these effects immunisation programmes have been considered in the context of an indefinite implementation period. The effective timescale for analysis is therefore set by the discounting practice. Using the current 3.5% discounting, means that the effective time scale is of the order of 30 years with significant contributions out to 60-90 years in the future. This is consistent with the period over which members of the working group intuitively believe that it is possible to make reasonable predictions of the future – in particular the current health ecology, both in terms of disease and mitigating technology.

36. - Implementing a 1.5% discount rate for health impacts (which will be the main impact of any immunisation programme) without explicitly using a separate timescale for analysis means that the characteristic period of analysis becomes about 65 years with significant contributions out to 130-190 years in the future. Looking back over similar periods shows that health ecology and technology have changed very significantly and it is problematic to take seriously contributions over this entire timescale.

37. - This problem is specific to immunisation programmes. In most health economic evaluations, the timescale is commonly bounded by the life expectancy of those being treated. In immunisation it is necessary to include all those born over the analysis period.

38. - The working group agreed that an explicit restriction of the analysis timescale would be desirable if possible to avoid unreasonable reliance on health impacts in the distant future – beyond any reasonable forecasting period (say 50-70 years). While there are a number of possibilities for dealing with the issue, no solution meets all the following desirable constraints:

    a) - The procedure was generally consistent with current Department of Health non-immunisation practice.
    b) - The procedure did not weight the long term future too highly.
    c) - The procedure was not simply the effective retention of 3.5% discounting by other means.
    d) - The procedure ensured that equal health-related quality of life losses at equal times are similarly valued.

e) - The procedure maintained the natural property that the impacts of the sequelae of a disease (including death) are independent of the route of calculation.

f) - The procedure was sufficiently simple to be transparent.

39. - Following extensive discussion, the working group came to the conclusion that there was no simple purely algorithmic methodological solution.

40. - The working group therefore advises that economic evaluations of immunisation programmes should be carried out at 1.5% discount rates for costs and benefits with an indefinite time horizon. The results would be considered 'conventional' in the sense that they would be consistent with other public sector appraisals that do not apply temporal weighting. A sensitivity analysis should be undertaken to highlight the extent to which the estimated cost-effectiveness is influenced by this choice of discount rate and time horizon. This would allow decision makers to investigate the role of conventional long term QALYs in the overall cost-effectiveness outcomes. The working group recognised that the JCVI was not constituted in a way to consider the issues without assistance and considered that guidance to the JCVI would be required on how to interpret the difference in results - in particular if a vaccine were cost-effective with the indefinite time horizon but not with one of, say, 50 years. It is suggested, in such cases that the timescale at which the vaccine becomes cost-effective be calculated and the JCVI would advise if it was reasonable to include effects on this timescale.

41. - Similarly, the DH would need to consider, on the basis of the JCVI advice, how 'conventional' QALY gains and losses in the distant future should be treated in setting the indicative prices used in the procurement process. For example, the Department might decide to use the results from application of an indefinite timescale when distinguishing between vaccines but include the uncertainty regarding the "conventional" QALY gains and losses in the distant future as part of the overall assessment.

42. - In cases of vaccine interaction it is recognised that it is necessary to investigate a range of different timescales of analysis even with the current 3.5% discounting. Indeed, the timescale may be critical to the cost-effectiveness or otherwise of a programme. For example, in the case of Varicella/Zoster in the short term increases in the number of Zoster cases may make the programme non-cost effective although in the longer term reduction in Varicella will lead to proportional reductions in Zoster. Such interactions will continue to require additional case by case treatment of time scales.

Recommendations

4.1 Immunisation programmes should be evaluated using an indefinite timescale and, as a sensitivity test, an analysis should be undertaken to highlight the extent to which the estimated cost-effectiveness is influenced by this choice of discount rate and time horizon.

4.2 Decision makers should be advised on how to interpret the difference between the two sets of results and the role of the QALY gains and losses in the far future in the difference between the results.

4.3 While review of procurement methodology is beyond the remit of this working group, the Department should give consideration to how uncertainty regarding cost-effectiveness, and specifically sensitivity analyses should be included in the procurement methodology.

Section 5: Relationship between cost and outcome

43. - In the case of vaccination there are a number of factors which influence the relationship between costs and outcomes. These factors are largely absent when evaluating new drugs but there are instance where the relationship between cost and outcome varies in the evaluation of surgery (e.g. learning effects) and diagnostic tests (e.g. relatively high fixed costs relative to variable costs).

44. - Incremental cost-effectiveness is likely to vary with output due to:

a) - Vaccine price may be a decreasing function of the quantity purchased (ICER probably falls as output increases).
b) - Diminishing returns to finding unvaccinated people (ICER probably rises as output increases).
c) - Herd immunity (ICER may have a complex relationship with changes in output).

45. - Effectiveness (and not just cost) will also vary by uptake. JCVI currently considers some of these issues, especially how effectiveness varies with uptake, but not in a systematic way. The extent of variation due to the above would vary by vaccine and disease covered (e.g., if it is an infectious disease). Within a season it would be difficult to stop vaccinating a population on equity grounds, especially those explicitly seeking to be vaccinated, even if it was not cost-effective to continue. Rational companies would account for the above non-linearities and price their product at the cost-effectiveness threshold, with this price being dependent on the quantity purchased.

46. - Epidemics may have an impact on the opportunity cost of not vaccinating. In the event of an epidemic (e.g., seasonal flu outbreak) the NHS might be overwhelmed, and non-marginal treatments (treatments with an incremental cost-effectiveness ratio well below the incremental cost-effectiveness threshold) may be displaced to make way for the treatment of epidemic victims. Hence, interventions to avoid epidemics might produce an additional benefit by avoiding non-provision of non-marginal treatments. Non-marginal treatments that would be displaced in an epidemic might be things like elective surgery, which could be delayed.

Recommendations

5.1 Cost-effectiveness analyses ought to consider systematically whether there are important non-linearities in costs, effectiveness and cost-effectiveness with

uptake/output due to factors such as, diminishing returns to finding unvaccinated people, and herd immunity, which need to be quantified.

5.2 Cost-effectiveness analyses of vaccination programmes ought to consider the impact of (avoiding) an epidemic on treatment of non-marginal cases such as postponement of treatment.

Section 6: Measuring and valuing health effects

47. - There are two main issues to address with respect to the measurement and valuation of health effects. The first concerns effects which might be relevant to a decision which are either not considered or are potentially inadequately captured. The working group considered two instances: unintended consequences of vaccination, specifically serotype replacement, and the suggestion that vaccines offer 'peace of mind' which may not be captured in the estimate of QALYs gained. The second issue relates to the valuation of health effects, and specifically whether the relative value placed on different effects is appropriate.

48. - In certain circumstances, and for certain diseases, vaccination can lead to a rise in other serotypes that are not being vaccinated against, increasing risks of disease from those serotypes. There are other potential negative impacts on population health that arise from vaccination programmes, such as increasing the average age at infection (where disease may be more severe) following infant vaccination (examples include rubella and chickenpox). Negative unintended consequences should be included in economic analyses of vaccination programmes, though they would not apply in every case. There is some empirical evidence to quantify the effects, but more research is needed.

49. - Is there an intangible 'insurance' benefit of vaccines due to 'peace of mind'? For example, might people value peace of mind knowing that they and their families are protected from a disease? This might be achieved not just from those who are vaccinated from a disease, but also others in the population.

50. - Five potential elements of benefit can be identified:

a) Direct health benefits from disease avoidance by vaccinated people.
b) Indirect health benefits from disease avoidance by non-vaccinated people via herd immunity.
c) 'Peace of mind' benefits to vaccinated people and their family.
d) 'Peace of mind benefits' to people protected via herd immunity.
e) A caring externality (positive consumption benefit) to those not protected by the vaccination programme.

51. - While vaccines (and prevention more generally) might be argued to be special because they provide non-health benefits, spending on vaccines/prevention displaces expenditure on treatment, and these may also have 'peace of mind' benefits (e.g., reassurance from knowing it is possible to access emergency care from an A&E

Department when needed). In this case vaccines might not be considered special. This is an area where the evidence base is very limited.

52. - While 'peace of mind' benefits and caring externalities (c to e above) may be obtained from any intervention it is unclear how the magnitude of these benefits for vaccines compare with other interventions; there is no evidence of public values.

53. - One difficulty with measuring 'peace of mind' benefits is that they may change over time, e.g., as visibility and perceptions of a disease change. 'Peace of mind' benefits are also likely to be related to the severity of the condition being prevented. Suppose vaccine A is for a disease that has a high probability of occurrence but the negative health consequences of getting the disease are small, and vaccine B is for a disease with a low probability of occurrence but the negative health consequences of getting the disease are large. Further assume that the expected QALYs gained from both vaccines are the same. 'Peace of mind' benefits are likely to be higher for B, and this is related to the severity of the disease in this case.

54. - These psychological benefits might not be captured by QALYs, leading to an underestimate of the benefits of vaccines. On the other hand, perhaps some dimensions of health-related quality of life do capture these effects (e.g., the anxiety and depression dimension of the EQ-5D instrument). If these potential benefits are unlikely to be captured in the standard QALY framework, one option would be to value benefits using willingness-to-pay in a CBA.

55. - NICE public health methodological guidance permits consideration of non-QALY benefits on a case-by-case basis so consideration of 'peace of mind' benefits outside of QALYs would not be inconsistent with other guidance.

56. - More research is needed to quantify the magnitude of 'peace of mind' benefits from different types of interventions and circumstances, and the materiality of including these benefits in an economic evaluation.

57. - The relative weight to place upon different health outcomes, while a long-standing area of research interest, has received increased attention in recent years in the discussions around value-based assessment.

58. - NICE have a number of special criteria which they, in effect, use to weight the formally estimated QALYs. Many of these simply take account of the possible underestimation of the QALY losses due to disease as measured by the EQ-5D questionnaire, for example, in the case of children. However, they also provide for the weighting of QALYs for end of life treatments and for diseases causing a large extended reduction in quality of life. NICE is currently considering, as part of Value Based Assessment, the possibility of taking account of both the absolute and relative reduction of quality of life from a disease, over the period of illness.

59. - Essentially, this is the question of whether and how to account for a sense in some quarters that the linear aggregation of QALYs fails adequately to capture society's objective in spending money to confer health.

60. - A summary of the AAWG position is that differential weighting of impacts should ideally be identical across programmes, should certainly be identical across evaluations within programmes and should be accounted for in a way that recognises the distribution of impacts among the displaced. However, the AAWG acknowledge that, in terms of the factors warranting differential weighting and the mechanisms for such weighting, there is not yet agreement on best practice. It suggests that best practice should include presentation of any available evidence on society's valuation and explicit calculation, presentation and recording of the implicit valuations that correspond to group decisions.

61. - The working group considered whether or not the evaluation of vaccines with respect to the weighting of different health benefits should differ from that of other programmes whose primary objective also involved improving or maintaining health. We concluded that since JCVI is a manifestation of the same society as other programmes, it pursues the same (albeit undefined) objective when spending money to confer health, or rather it cannot justifiably pursue another objective.

62. - The question becomes the extent to which JCVI should argue for the use of special criteria and, if so, which ones, based on its expertise, experience and deliberations on the nature of vaccine preventable disease. As noted previously, it has been suggested that vaccine preventable disease is often severe and often affects children. The discussions held by the working group suggested a view that this distinguished vaccine preventable disease in important ways beyond the non-health and family/carer impacts.

63. - Discussion suggested that 20 QALYs lost, restored, or not lost in the first place in one person is considered of more intrinsic worth than 0.002 QALYs in each of 10 000 people, at least among working group members. We also discussed whether a QALY lost, restored, or not lost in the first place in a child is considered of more intrinsic worth than that in a young adult, a middle aged person or an older person. The general conclusion was that more evidence is required regarding the values of society at large.

64. - The prospect of NICE including in evaluations an assessment of both the absolute and relative QALYs lost or gained was not discussed explicitly by the working group. However, if the beneficiaries of vaccine programmes are often those with poor baseline health (and more often so than for displaced interventions) the consideration of relative QALY losses could potentially be important for JCVI.

65. - However, this would have to flow from a finding that society at large (rather than the beneficiaries) values a QALY more if conferred upon someone with a lower health status. If an assessment of society's view on this comes from how changes in measured quality of life is experienced by those gaining or losing through allocative

decisions, then a potentially complicating feature of vaccinations is that QALYs are not restored but rather not lost in the first place. Additionally, it was noted that it is not analytically straightforward to identify the health characteristics of the likely beneficiaries of a vaccine programme.

Recommendations

6.1 Cost-effectiveness analyses ought systematically to consider unintended consequences of vaccination programmes, including serotype replacement.

6.2 Research needs to be undertaken regarding 'peace of mind' benefits. Until there is such clear evidence a very strong specific case would need to be made as to why a particular programme ought to be treated differently by including such non-QALY benefits.

6.3 The working group recommend that JCVI should follow emerging best practice in terms of how it presents and records any value judgements it makes when applying differential weights, acknowledging that past decisions do not (of themselves) constitute an evidence base for future decisions.

6.4 Where differential weighting of QALYs is generally recommended because of the perceived failure of instruments to capture quality of life in specific groups (for instance children) JCVI should follow emerging best practice, applying any adjustments to impacts of the vaccine under evaluation and of displaced activity.

6.5 JCVI should communicate to AAWG its position on what factors warrant differential weighting within evaluations of health interventions.

6.6 JCVI should follow with interest the deliberations of other bodies including AAWG on how to consider relativistic effects when evaluating the gain or loss of QALYs, with a specific attention on how prevention of QALY loss fits into any theoretical framework that emerges.

Section 7: Appraisal of evidence

66. - Given the available information regarding the costs and effects associated with a particular immunisation programme there are a number of issues with respect to the appraisal of evidence by decision makers. First, how large must the incremental benefit be relative to the incremental cost for a vaccine to represent good value for money for the NHS? Second, not all decisions involve the introduction of programmes, there are also decisions to be taken regarding whether or not to disinvest in a particular programme. Does disinvestment in immunisation programmes raise any special considerations? Third, how is the inevitable uncertainty regarding the costs and the effects associated with an immunisation programme to be addressed within the decision making process? Fourth, how should we account for uncertainty in the timing and magnitude of epidemics?

Valuing health displaced by expenditure on immunisation

67. - Adoption of new health care programmes will generally result in the displacement of health care activities that would otherwise have been undertaken. Organisations represented by the AAWG have considered alternative methods for valuing displaced health when appraising interventions in health and social care. Two broad and potentially related methodological approaches have been considered by these organisations. The first approach involves the application of a cost-effectiveness threshold (typically a cost per QALY threshold) in a manner that internalises reflection of opportunity costs. The second approach attempts to explicitly value health displaced using calculations of incremental cost at which a QALY is gained or displaced in the NHS. It explicitly reflects the opportunity costs of new adoption decisions. The two approaches differ not only in terms of how they consider opportunity costs, but in how they incorporate non-QALY factors in the calculus. In the first approach, additional aspects of value associated with the programme under appraisal can be reflected by adjusting the cost-effectiveness threshold. In the second approach, additional aspects of value should be reflected by calculating them separately, and adding them to the total costs and benefits of the programme.

68. - Most organisations represented by the AAWG continue to apply a cost-effectiveness threshold as the defining decision rule in their decision-making. For example, the NICE technology appraisal programme applies a range of cost-effectiveness thresholds: (i) £20,000 per QALY (basic threshold); (ii) £30,000 per QALY (notional upper limit of threshold range); and (iii) £50,000 per QALY (threshold applied to life-extending end of life drugs). The cost-effectiveness thresholds applied by decision-makers have evolved rather than being determined by a definitive process. An early methodology document produced by a NICE working group summarised four broad approaches that could be used to identify the appropriate value for the cost-effectiveness threshold: (i) establishing society's willingness to pay for health gain; (ii) setting the threshold equal to gross domestic product per head of population; (iii) setting the threshold equal to the value of life/health used in other public sector decisions; and (iv) setting the threshold to exhaust the health budget optimally (an early theoretical framework for valuing health from displaced activities). The working group considered that decision rules informed by these approaches provide an inadequate basis for quantifying and valuing health displaced by new immunisation programmes.

69. - In recent years, health economists based at the Centre for Health Economics, University of York, have undertaken a programme of work broadly aimed at informing the value of the cost-effectiveness threshold used by NICE. The seminal report produced by these researchers estimated the impact of marginal increases or decreases in overall NHS expenditure in several programme budget categories on mortality outcomes and, by extension, QALYs. The econometric methodology provides an empirically-based and explicit quantification of the scale of opportunity costs the NHS faces when considering whether the health benefits associated with new technologies are expected to offset the health that is likely to be foregone elsewhere in the NHS. The methodology falls under the second approach outlined in the first paragraph of this section. It offers the benefit of informing the value of the cost-

effectiveness threshold that could be used across the NHS. The most relevant 'central' threshold estimated by the researchers was £12,936 per additional QALY, denominated in 2008 prices.

70. - The working group noted that on the basis of the programme of work by the York researchers, the DH is now recommending that the opportunity costs of spending from the NHS budget, in terms of displaced health, are estimated using a figure of £15,000 per QALY. To arrive at this figure, the York estimate was adjusted with the GDP deflator to £14,803 in 2014/15 prices. For convenience, and for the time being, the DH recommends that this figure is rounded to £15,000 per QALY for use in DH Impact Assessments.

71. - The York research has been criticised by the Office of Health Economics (OHE) and the industry and patient group stakeholders. The crux of these criticisms revolves around the data available to the researchers and the sensitivity of their results to their underpinning assumptions. With regard to the available data, the OHE and the industry and patient group stakeholders focussed their criticism in two areas: (i) the units of analysis (primary care trusts (PCTs)) may systematically differ in their decision making, e.g. for historical reasons; and (ii) the health-related quality of life component of the estimated QALYs may have been based on an incorrect assumption about the relative skill of PCTs in improving health-related quality of life versus reducing mortality. The OHE and the industry and patient group stakeholders questioned the assumptions that: (i) patients whose lives are saved will live as long as healthy people of the same age; and, (ii) that these patients will enjoy better health-related quality of life than the average patient with the same disease. The industry and patient group stakeholders also noted that the current Pharmaceutical Price Regulation Scheme (PPRS) for medicines fixes the cost-effectiveness threshold used by NICE until 2019, and early adoption of the York-informed threshold may place new immunisation programmes at a comparative disadvantage. The working group recognises the limitations of the York models, but feels that Claxton and colleagues have made best use of existing evidence, and provided interpretations that are careful and balanced. DH have commissioned further empirical work in this area and it will be closely monitored by the AAWG.

72. - The working group considered whether there is any theoretical and/or empirical evidence to suggest that a different cost-effectiveness threshold should be applied to immunisation programmes compared to other areas of health care. No theoretical or empirical evidence could be identified to support such a case. Indeed, it was felt that even if data were available to inform an immunisation-specific cost-effectiveness threshold, it is likely to result in sub-optimal levels of population health.

73. - The working group recognised that there are likely to be transitional issues whilst drugs bought via the PPRS agreement are currently assessed against a NICE threshold of £20,000 per QALY but with a fixed total budget while, on the other hand, the Department of Health now uses the £15,000 figure in its assessments.

74. - A system that relies on the cost-effectiveness threshold should be predicated on the assumption that the threshold reflects the economic value of health displaced by a health care programme. The recent research by health economists at the University of York to estimate economic values for the cost-effectiveness threshold attempts to reflect the displacement implications of adoption decisions and the magnitude of the health forgone. This framework is not considered to be compatible with individual or group based equity weights, for example age weights, or indeed any other system of weighting which depends on characteristics other than patient programme budgeting categories predicated on primary clinical diagnosis. Therefore unitary (unweighted) values for health impacts, for example QALY impacts, should be applied within economic evaluations of immunisation programmes.

75. - DH guidance suggests that in the long term (beyond 10 years) the conversion factor between DH expenditure and QALY gains and losses, i.e. the cost effectiveness threshold, should rise by 2% per annum:

Extract from current DH impact assessment guidance:

199. - In the long run, the real cost per QALY at the margin in the NHS is expected to rise in line with per capita GDP (2% p.a., balancing the expected drop in the marginal utility derived from other goods as consumption increases). However, given general austerity, the recommended default assumption for policy interventions with impacts lasting up to 2023 is that the cost per QALY at the margin in the NHS will be constant in real terms.

200. - There are uncertainties around the future trajectory of the threshold and indeed over the current estimate. However, for practical purposes the above trajectory should be used pending updated empirical estimates.

201. - The value of net production impacts will however in general be expected to rise in line with real GDP per head (around 2% p.a.), as discussed previously.

202. - Note that this projected path of the opportunity cost of NHS and DH funds (i.e. how much benefit is derived from marginal spending) is a pragmatic simplifying assumption rather than a prediction or a commitment.

76. - The working group does not consider that the threshold should be assumed to change in this manner. We have considered the empirical evidence for the changes in the cost-effectiveness threshold and do not believe that there is an empirical basis for the DH's assumption. Indeed, even after the adoption of a £15,000 per QALY threshold some evidence suggests that the optimal threshold value may need to fall over time assuming medical innovation continues at roughly its current rate.

77. - We also believe that there is a theoretical difficulty with the DH's argument. The 'threshold' applies to the QALY cost in health budget expenditure pounds - whereas the GDP impact should affect social value. There is only a loose relation between the two (they differ by a factor of 4 on evidence currently accepted by the DH) and the threshold, although not independent of GDP, has traditionally depended on other factors, including politically decided factors.

78. - There are also practical considerations. The use of an increasing threshold is mathematically equivalent to differential discounting of costs and benefits. Such differential discounting introduces the need to introduce sophisticated decision criteria. These have not been developed for immunisation programmes. Although the literature notes the problem and observes that many of the most discussed problems disappear if considered in terms of net-benefit rather than the cost-effectiveness ratio, the essential point remains that the naive decision rule, i.e. that a programme is cost-effective if the Net Benefit is positive, leads to contradictory results depending on the route of calculation.

79. - Given most programmes considered by DH only have cost schedules of less than 10 years the DH would be unlikely to take account of the threshold change in the way described in the Guidance.

80. - Given the lack of empirical evidence, the theoretical difficulties and the incomplete analytical framework we do not consider that the threshold should be considered to increase. Rather we recommend that should the threshold be increased in fact, the cost-effectiveness of programmes previously rejected should be reviewed. The working group understands that the AAWG has come to similar preliminary conclusions.

Disinvesting in vaccination programmes

81. - Are there factors, peculiar to vaccines that ought to be taken into account when considering disinvestment in a vaccination programme?

82. - Issues of disinvestment in health care programmes usually arise because an intervention is no longer cost-effective relative to a comparator. In the case of vaccines disinvestment is usually considered when disease incidence falls to very low levels. Decisions to fund vaccination programmes are long-term decisions – it is difficult to turn vaccinations programmes 'on and off' from one year to the next.

83. - A cost-effectiveness analysis should include the expected effects of disinvestment. For example, if a disease were likely to return at a future date if a vaccination programme were to be discontinued then the expected consequences should be incorporated into the analysis.

84. - A purely quantitative analysis focusing on costs and QALYs might lead to conclusions which are impractical or undesirable to implement. An example might be a proposal to repeatedly switch a programme on and off as prevalence changes, without full regard for political, administrative or fairness considerations. Ideally these broader factors would be quantified and included in an economic analysis, but this may not always be feasible. This problem may be minimised by careful identification of the options to be compared, and by routine consideration of a range of factors in addition to economic factors.

85. - When considering disinvestment the following cases might arise:

a) - A disease has not been eliminated, but incidence is low due to the success of the vaccination programme. In this case disinvestment would probably not be warranted as the disease is likely to return.
b) - There is declining incidence of disease due to underlying epidemiological factors not directly related to the vaccination programme. Disinvestment may be considered, first by considering reduced provision only in lower-risk sub-groups.
c) - There is evidence of low incidence of disease, but this has a random component, and the disease may come back if the vaccination programme is discontinued. If disinvestment occurred then it may not be possible to reinstate the vaccination quickly enough if the disease re-emerged. Disinvestment would need to be carefully considered in this case.
d) - Advances in treatment mean that a disease can be effectively, easily and cheaply treated when it arises symptomatically. In this case the value of prevention may be diminished and disinvestment may be considered.
e) - A vaccine is less effective or more costly than originally expected, e.g. due to uncertainties in the epidemiological, cost and effects data in the original economic analysis. In this case the value of the programme may be diminished and disinvestment may be considered.

86. - Subject to other CEMIPP recommendations, standard rules for investing in a new vaccination programme are likely to be: (a) a 'point estimate' test (incremental cost per QALY gained less than £15,000 or other value indicated by additional research); and, a 'harm to the NHS' test (incremental cost per QALY gained must have no more than a 10% chance of exceeding £25,000).

87. - The point estimate for disinvestment should generally be the same as the point estimate for investment, so that the decision rules are consistent and symmetrical with regard to the value of displaced activities. However, decisions to disinvest (and especially close decisions) would be taken by ministers, informed by the JCVI, and other factors might be taken into account, such as context, policy, and epidemiological factors.

88. - In terms of combining the 'point estimate' and 'harm to the NHS' tests to disinvesting in vaccination programmes, there are three options:

(i) - Apply the same rules and tests as if it was being decided whether or not to continue to invest in the programme. In this case if either or both tests fail then the programme should be discontinued.

(ii) Apply the point estimate test only, with careful consideration of the harm to the NHS test, but without a formal rule.

(iii) Consider the disinvestment decision as a new investment decision, with the option of retaining the programme as the comparator, and then estimating the 'point estimate' and 'harm to the NHS' tests for the decision to disinvest relative to this.

89. - In the case of option (i), candidate programmes for disinvestment are most likely to fail the 'harm to the NHS' test, and this may put too much weight on the uncertainty inherent in disinvestment decisions, and treat it too inflexibly. On the other hand, option (iii) would create an unintended incentive not to reduce uncertainty, i.e., high uncertainty about the costs and benefits of disinvesting might discourage disinvestment, and hence lead to retention of uncertain programmes. Option (ii) seems a sensible compromise, as it would allow some flexibility in the treatment of uncertainty, but ought not to provide any perverse incentives not to reduce uncertainty.

90. - Disinvesting in a vaccine programme should rarely be considered as a 'yes/no' decision. One option that should also be considered is the partial withdrawal of the programme so it is retained in some sub-groups of the population (e.g., high risk sub-groups). Another option could be to recommend continued provision providing it can be procured at a lower vaccine price. This possibility ought to be considered when the options to be compared in the economic analysis are being determined.

Accounting for uncertainty in the timing and magnitude of epidemics

91. - CEMIPP was of course aware of the report of the Working Group on Uncertainty in Vaccine Evaluation and Procurement (WGUVEP) issued in 2012. While it was recognised that explicitly revisiting the deliberations of WGUVEP was not necessarily a good use of CEMIPP time some consideration of uncertainty was inevitable. In the end the recommendations of WGUVEP were thoroughly discussed but the only specific recommendations made were with respect to revising WGUVEP guidance to reflect changing views regarding the opportunity costs of spending from the NHS budget in terms of displaced health.

92. - Decisions to fund vaccination programmes are long-term decisions – it is difficult to turn vaccinations programmes 'on and off' from one year to the next. Hence, even if it was felt that an epidemic might not occur in one year provision would still go ahead. Therefore, cost-effectiveness needs to be judged over a time period longer than one year, accounting for the expected value of an epidemic occurring each year. JCVI currently does this.

93. - New epidemiological data are produced each year and there is currently no formal assessment of the likely impact of this on cost-effectiveness. This raises the question as to how often the cost-effectiveness estimates for a vaccination programme ought to be reviewed and updated by JCVI.

94. - The workload in undertaking a full review of cost-effectiveness should be balanced against the likelihood of its altering policy in any way. This likelihood will depend on the availability of new information affecting costs and outcomes of the vaccination programme and the resultant size and direction of any change in cost effectiveness.

95. - A report was produced by the WGUVEP with the aim of providing technical advice and more general expert opinion on issues surrounding uncertainty in vaccine evaluation

and procurement. Its recommendations were based on the assumption that a cost-effectiveness threshold of £20,000 per QALY reflected the best estimate of opportunity cost elsewhere in the NHS of allocating resources to immunisation programmes. This working group recommended that evaluators (taking account of JCVI advice) should be 'almost certain' that the incremental cost-effectiveness ratio is less than £30,000 per QALY (NICE's upper limit of threshold range). More specifically, the recommendation was that when assessing parameter or structural uncertainty, 95% (subsequently revised to 90%) of scenarios in a Monte Carlo simulation fall below a £30,000 per QALY threshold. This criterion was designed to limit the harm to the health system should the most plausible estimate of cost effectiveness be optimistic. In principle it depends on distributional factors and the level of acceptable harm. The York analysis described above does not impact on the distributional considerations but does on the level of harm. In the light of our recommendation that the opportunity costs of investment in immunisation programmes should now be estimated using a figure of £15,000 per QALY, the upper limit of the previous threshold range should be revised downwards in the uncertainty analyses to £25,000.

Recommendations

7.1 DH advised by the JCVI should continue to judge cost-effectiveness over a minimum time horizon of 10 years accounting for the expected value of an epidemic occurring each year. A review of any changes in evidence relevant to cost-effectiveness ought to be undertaken periodically during this period (e.g., every five years) and if appropriate a formal updating of the estimates of cost-effectiveness should be commissioned.

7.2 The opportunity costs of investment in immunisation programmes, in terms of displaced health, should be estimated using a figure of £15,000 per QALY. This value to be re-assessed as additional relevant research becomes available.

7.3 The cost-effectiveness threshold should be considered to remain at its newly recommended value (£15,000 per QALY) through the economic evaluation supporting a decision on an immunisation programme. If the threshold changes in the future, the status of current immunisation programmes and those rejected on cost-effectiveness grounds should be reconsidered.

7.4 When considering disinvesting in a vaccine programme on cost-effectiveness grounds the 'point estimate' test ought to be applied, with informal consideration of the 'harm to the NHS' test (option (ii) above). However, decisions to disinvest should not be made based on purely quantitative economic analyses focusing on costs and QALYs; political, administrative and fairness considerations ought to be taken into account, along with careful consideration of the options to be evaluated.

7.5 Research is required that would increase our understanding of incorporating equity concerns, for example, equity weighting of health benefits foregone as a result of activities displaced by immunisation programmes.

7.6 In order to assess whether the risk of an immunisation programme being not cost-effective is acceptable, the JCVI should require that 90% of scenarios in a Monte Carlo simulation fall below a £25,000 per QALY threshold.

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96. - CEMIPP would like to thank the many members, contributors, peer reviewers and wider stakeholders who have contributed their advice and help during this review. Their support has been invaluable. A full list of those who have contributed to this review is annexed below.

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ANNEX A List of contributors

The conclusions and recommendations of the CEMIPP review have drawn on the invaluable advice and contributions of the following. Individuals may hold differing views on particular issues and this list is provided more to acknowledge the help provided, than to imply only one view of the many complex issues is possible.

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