NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal

Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of NICE technology appraisal guidance 67)

The table contains summaries of comments received in response to consultation on the ACD and received via the NICE website and in writing from the public.

Comment from	Nature of comment	Response
Roche	1. WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT Roche believe that the majority of relevant evidence has been taken into account in this appraisal. However Roche feel that the extent to which the Appraisal Committee took into account some of the evidence and feedback submitted on the Assessment Report is unclear. Little emphasis seems to be given to the majority of the points made by Roche in response to the Assessment Report and so the key messages from our previous response are attached again here, in Appendix A. Roche believes that these issues (Preventative efficacy of vaccination; Assumed number of GP visits; Probability of hospitalisation; Estimated drug costs; Probability that patients present within 48 hours; Practical implementation of the Assessment Report findings; and Budget impact estimates) are worthy of detailed consideration by the Appraisal Committee. Failure to consider this evidence would represent a weakness in the technology appraisal. An important overarching issue in this appraisal which has not been taken into	The Appraisal Committee considered the issues raised in response to the assessment report at the first meeting. The Committee agreed with the Assessment Group's estimates of efficacy of vaccination (4.3.2, 4.2.7) and assumed number of GP visits (4.3.8) and accepted the methodology of the modelling (4.3.9). Implementation and budget

Comment from	Nature of comment	Response
	account in the evidence used to formulate recommendations relates to the dynamic benefits of prophylaxis treatment of influenza. Dynamic benefits are not included in the Roche or the Assessment Group's economic model. No benefits associated with preventing transmission of influenza from the person who receives prophylaxis that avoids infection, to others who may have contracted the illness from this person are included in the analysis. Such dynamic effects would increase the QALY gain associated with prophylaxis and would also reduce NHS resource use due to avoided influenza. Technically and computationally including such benefits is difficult and Roche believes that the cost effectiveness of oseltamivir can be demonstrated without a dynamic model. However, because the Assessment Group's results show higher ICERs than the Roche model, taking oseltamivir over the cost effectiveness threshold on some occasions, taking account of the dynamic effects becomes very important. Including dynamic effects in an economic assessment would reduce the ICERs associated with oseltamivir for all treatment groups and the Appraisal Committee should consider taking this into account in their deliberations.	impact are not within the remit of the Appraisal Committee. The Committee discussed the limitations of the models from which the cost-effectiveness evidence was derived. It was aware that a dynamic model would include benefits that would make the interventions more cost-effective (as suggested) but also disbenefits that could worsen cost-effectiveness. It concluded that on balance an alternative dynamic modelling approach would not have changed its overall conclusions (see FAD 4.3.9).
Roche	2. WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE Roche considers that the current interpretations of the evidence by the Appraisal	

Comment from	Nature of comment	Response
	Committee are not always appropriate and in line with the usual classification of cost effectiveness by NICE and it is presently unclear why this is the case. Roche feel that the cost effectiveness results of the Assessment Group's report have not been adequately reflected in the Appraisal Committee's provisional recommendations given the convention that interventions associated with incremental cost effectiveness ratios (ICERs) of less than £30,000 are considered cost effective and recommended for use within the NHS. For a number of patient groups, oseltamivir and zanamivir have not been recommended despite the Assessment Group estimating cost effective ICERs. These patient groups are discussed below.	Please see 'Guide to the Methods of Technology', Appraisal, April 2004, sections 6.2.6.10 and 6.2.6.11 for the Committee's approach to ICERs above £20,000 and £30,000.

Comment from	Nature of comment	Response
Roche	**Post-Exposure Prophylaxis - Healthy Unvaccinated Children** The Assessment Group estimate an ICER of £23,225 for zanamivir compared to no prophylaxis for these patients. Oseltamivir is associated with very slightly less QALYs for this patient group compared to zanamivir (0.0032 QALYs lost compared to 0.0029), but this is at lower cost (£54.35 compared to £61.18). Hence the cost effectiveness results for oseltamivir and zanamivir are very similar for these patients compared to no prophylaxis. Using the figures presented by the Assessment Group, the ICER for oseltamivir compared to no prophylaxis can be calculated as £23,593. Given that the Appraisal Committee has accepted that it is not possible to differentiate between the efficacy of oseltamivir and zanamivir (therefore equal efficacy should be assumed) the ICER for oseltamivir should be even lower. Therefore both oseltamivir and zanamivir have ICERs of well below £30,000 for these patients, reflecting a cost effective use of NHS resources. In addition, table 75 in the Assessment Group's report states that at a cost effectiveness threshold of £30,000 there is a 45% probability that zanamivir will be the most cost effective treatment, a 40% probability that oseltamivir will be the most cost effective treatment, and only a 15% probability that no prophylaxis will be most cost effective. Therefore despite a combined probability of 85% that either zanamivir or oseltamivir will represent the most cost effective treatment in this patient group neither treatment has been recommended by the Appraisal Committee and no reason has been given for this omission.	The price of zanamivir has been reduced and it was assumed that both drugs were of equal efficacy (4.3.12) The Committee noted that healthy children are not usually recommended vaccination and would therefore not normally be considered for drug prophylaxis. The Committee did not accept the argument that the decision should be based on the probability of anti-viral prophylaxis with either drug being the most cost-effective option, calculated by summing up the probabilities of multiple options. Please see 'Guide to the Methods of Technology', Appraisal, April 2004, sections 6.2.6.10 and 6.2.6.11 for the Committee's approach to ICERs above

Comment from	Nature of comment	Response
		£20,000 and £30,000.
Roche	**PEP - At Risk Vaccinated Children** The ACD only recommends oseltamivir or zanamivir for these patients if a child is not adequately protected by vaccination. However the Assessment Group estimate an ICER of below £30,000 for *all* at risk vaccinated children. In a similar way as for healthy unvaccinated children, the cost effectiveness results are very similar for oseltamivir and zanamivir. Zanamivir has an ICER of £27,684 compared to no prophylaxis, and the figures quoted by the Assessment Group mean that oseltamivir has an ICER of £29,062 compared to no prophylaxis. Again, assuming equal efficacy between oseltamivir and zanamivir as accepted by the Appraisal Committee would result in a lower ICER for oseltamivir. Table 75 in the Assessment Group's report shows that at a cost effectiveness threshold of £30,000 there is a 31% probability that zanamivir will be the most cost effective treatment, and a 29% probability that oseltamivir will be the most cost effective treatment for these patients, representing a 60% probability that either oseltamivir or zanamivir will be the most cost effective use of NHS resources. There is only a 39% probability that no prophylaxis will be cost effective for these patients. Therefore again both treatments have mean ICERs and probabilistic sensitivity analysis results that would usually be accepted to represent a cost effective use of NHS resources, but the Appraisal Committee has not reflected this in their recommendations as yet. Again no reason has been given for this.	As above.
Roche	**Summary of Evidence for Healthy and At Risk Children** When considering the modelling results for healthy and at risk children the Appraisal Committee must consider that data for zanamivir is extrapolated from data in adults, while data for oseltamivir is taken directly from the relevant population. The modelling performed by the Assessment Group in the PEP setting for healthy children and at risk children has shown amantadine and oseltamivir to be dominated	Noted. The Committee considered that both oseltamivir and

Comment from	Nature of comment	Response
	by zanamivir. Upon reviewing table 32, page 150, it would appear that the Assessment Group have accepted the relative risk of contracting influenza following PEP for oseltamivir in healthy children and at risk children to be 0.36 and 0.36 respectively. The RRs of 0.36 have been derived from sub-group analyses of the paediatric group from the household study by Hayden et al (2004) as stated in the report section 5.2.2.2.2, page 84. However, the RR used for the paediatric groups when modelling zanamivir were taken from the mixed group studies of adults and children from Hayden (2000), Kaiser (2000) and Monto (2002) with no specific sub-group analyses performed for the paediatric groups. As increased viral shedding is well-documented in the paediatric setting with expected lower efficacy of anti-virals compared to the adult setting, it would be inappropriate and inconsistent to extrapolate data from mixed paediatric and adult data to the paediatric groups for zanamivir and use the paediatric specific data for oseltamivir. Therefore to apply mixed adult/paediatric efficacy data to represent paediatric efficacy biases this analysis in favour of zanamivir. Roche would suggest that sub-group analyses are performed in the defined paediatric setting using the databases that informed the Hayden (2000), Kaiser (2000) and Monto (2002) studies to enable a less biased comparison to be made between the anti-virals within the paediatric setting. Alternatively, Roche would suggest using the adult oseltamivir RRs for paediatrics to ensure a like for like comparison of the efficacy of the anti-virals. The Roche model assumed that oseltamivir and zanamivir were equally effective in influenza prophylaxis. This assumption was based in part upon the available evidence – as the table above highlights there is very little difference in the preventative efficacies across oseltamivir and zanamivir – and in part due to expert clinical opinion at a UK Advisory Board. It was generally felt by the attendees that oseltamivir and zanamivir are equally effective in influenza prophylaxis. This assumption is key in determining the most realistic cost effectiveness estimates	zanamivir were of equal efficacy and that the choice between them would be governed by the individual circumstance (FAD 1.2) The Committee's approach to thresholds is detailed in section 6.2.6.10 of the Methods Guide. 2004. The Committee did not consider it was appropriate to recommend prophylaxis in healthy children who would

Comment from	Nature of comment	Response
	for these patient groups. Adjusting the Assessment Group's economic model so that it assumed equal efficacy between oseltamivir and zanamivir should result in reducing the ICER for oseltamivir and as such the probability that oseltamivir is the most cost effective treatment option in these patient groups would increase. Taking this into account Roche believes that the non-recommendation of oseltamivir for healthy unvaccinated children and at risk vaccinated children is not supported by the evidence. This is a particular concern because the reasons for this decision have not been made clear by the Appraisal Committee.	not be considered for vaccine prophylaxis (see 4.3.11 of the FAD).
Roche	**Seasonal Prophylaxis - At Risk Unvaccinated Children** For this patient group the Assessment Group estimate an ICER of £16,630 for seasonal prophylaxis with oseltamivir compared to no prophylaxis. The Appraisal Committee note in the ACD that oseltamivir is not recommended in this population because of uncertainties surrounding the clinical inputs in the economic model. However it is Roche's belief that the results of the economic modelling are by definition the best informed estimate possible for each population. The rationale for undertaking economic analyses is to inform decision makers through use of the best clinical and economic evidence available, incorporating any uncertainty within the analysis (primarily through the use of probabilistic sensitivity analysis). Therefore to disregard economic evidence due to uncertainty is to disregard the best evidence available and instead to rely on judgement which by definition is associated with far more uncertainty than the economic analysis. The probabilistic sensitivity analysis conducted by the Assessment Group illustrates that with an ICER threshold of £20,000 there is a 70% probability that oseltamivir is the cost effective treatment option for seasonal prophylaxis of at risk unvaccinated children. This rises to 94% at an ICER threshold of £30,000. Roche believes that this represents strong evidence that oseltamivir should be recommended for this population group. It is Roche's belief	The Committee considered that the estimated ICER for this subgroup was unreliable as it was based on an attack rate and estimate of clinical efficacy that lead to an underestimation of the ICER. (FAD 4.3.10) The Committee does not disregard economic evidence where there is uncertainty but is cautious where the degree of uncertainty makes the evidence an unreliable basis for decision making.

Comment from	Nature of comment	Response
	that the ACD is too narrow in the patient populations for which oseltamivir is recommended in some instances. These are discussed below.	
Roche	**Seasonal prophylaxis - Healthy and At-Risk Vaccinated Elderly** The ACD only recommends oseltamivir for the vaccinated elderly population in a residential or nursing home setting when there is a localised outbreak of influenza. The ICERs estimated by the Assessment Group for oseltamivir compared to no prophylaxis are £28,473 for the healthy vaccinated elderly and £21,608 for the at-risk vaccinated elderly. Table 75 in the Assessment Report shows that for the at-risk vaccinated elderly there is a 78% probability of oseltamivir being the most cost effective treatment, given a cost effectiveness threshold of £30,000. For the healthy vaccinated elderly there is a 50% probability that oseltamivir represents the most cost effective treatment option, compared to a 47% probability that no prophylaxis is most cost effective. Therefore based on the ICERs and probabilistic sensitivity analysis presented by the Assessment Group Roche believes that oseltamivir should be recommended for all elderly people whether or not they have been vaccinated and whether or not they live in a residential or nursing home, when influenza is circulating. The ACD does not explain why this recommendation is not made.	The ICERs referred to here are for post-exposure prophylaxis. The ICERs referred to are above the threshold referred to the Methods Guide section 6.2.6.10. The committee's decision on the acceptability of the technology in such cases usually makes explicit reference to other factors. For these ICERs one such other factor is the management of an outbreak within a predominantly elderly population in a residential setting. The intervention is recommended in such cases see FAD section 4.3.13. Please see 'Guide to the Methods of Technology',

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		Appraisal, April 2004, sections 6.2.6.10 and 6.2.6.11 for the Committee's approach to ICERs above £20,000 and £30,000.
Roche	3. WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS As highlighted above the cost effectiveness results of the Assessment Group's economic model are very sensitive to changes in a number of assumptions. A change in a combination of these assumptions would considerably impact the final incremental cost effectiveness ratios. In addition it is an overarching issue that neither the Roche economic model or the Assessment Group model consider any benefits associated with preventing transmission of influenza from the person who receives prophylaxis that avoids infection, to others who may have contracted the illness from this person. Including this dynamic effect in an economic assessment would reduce the ICERs associated with oseltamivir for all treatment groups. Therefore all recommendations made in situations where the ICER is close to the cost effectiveness threshold should be made with this in mind. As stated in Roche's response to the Assessment Group's report considering multiple GP prescriptions per consultation – a very plausible assumption as explained in Appendix A, part (i) – also substantially reduces ICERs and the cumulative effects of these issues must be considered by the Appraisal Committee. It is Roche's belief that the sensitive assumptions and the dynamic nature of prophylaxis in this setting have not been considered in enough detail by the Appraisal Committee and further discussion should take place on this.	The Committee did not consider it appropriate to accept multiple prescriptions per GP visit (4.3.8).

Comment from	Nature of comment	Response
	In addition, the traditional cost per QALY decision rule does not seem to have been implemented in a consistent manner by the Appraisal Committee and therefore the provisional recommendations are not wholly suitable as a basis for guidance to the NHS. [Appendix A has not been reproduced in this table – for full consultee and commentator comments on the Appraisal Consultation Document, see the NICE website]	
GSK	GlaxoSmithKline have no comments on the Appraisal Consultation Document for the Prophylaxis of Influenza at this time, nor did we notice any factual inaccuracies in the report. We feel the ACD fairly balances the important role of the neuraminidase inhibitors in flu prevention in selected patient groups, against both the need to support the vital work of flu vaccination as a first line strategy, and the need to use NHS resources in a cost-effective manner	Noted
British Thoracic Society	*Do you consider that all the relevant evidence has been taken into account?* The summary covers the available trial data. The consultation document does not appear to have taken into account the submissions by both the HPA and the BTS regarding out of season outbreaks of influenza in closed communities and we would urge the Committee to carefully reconsider these comments. The clinical trials on the efficacy of neuraminidase inhibitors were conducted in years of low influenza activity when compared to the activity seen during the majority of the 20th Century. If influenza activity returns to more “normal” levels the cost benefit ratio of the drugs may alter substantially.	The Committee did make a specific recommendation to cover the situation described here (See FAD 1.6). The reasons for doing so are specified in 4.3.13. There have been amendments to this recommendation in response to the comments raised during consultation.
British	*Do you consider that the summaries of clinical and cost effectiveness are reasonable*	

Comment from	Nature of comment	Response
Thoracic Society	*interpretations of the evidence and that preliminary views on the resource impact and implications for the NHS are appropriate?* The current definition of at risk groups for influenza is broad and encompasses a spectrum of susceptibility from healthy individuals over the age of 65 to individuals with major immunosuppression (for example individuals undergoing chemotherapy treatment, bone marrow transplantation or with advanced HIV infection). The clinical trials on the efficacy of Amantadine, oseltamivir and zanamivir were principally conducted on healthy individuals or those with "more usual" at risk factors for influenza, and the guidance is sound in these settings. There is however little information on the use of these drugs for influenza prophylaxis in very high risk individuals and while research is urgently needed in this area some dispensation should be considered that would allow the use of neuraminidase inhibitors in such very high risk individuals. The cost of neuraminidase inhibitor prophylaxis is minor in this setting particularly when compared to the cost of antibiotics and anti-fungal agents used for example in bone marrow transplant or chemotherapy recipients with fevers.	The guidance is based on the available evidence and applies to the particular population subgroups. People with major immunosuppression are considered 'at-risk' and eligible for PEP if unvaccinated. All NICE guidance is within the context that 'health professionals are expected to take it fully in to account when exercising their clinical judgement' but the guidance 'does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient,…'
British Thoracic Society	*Do you consider that the provisional recommendations for the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance for the NHS?* As noted above the committees recommendation for the use of neuraminidase inhibitors are sound for the majority of clinical circumstances but do not cover out of season outbreaks in closed communities, nor the issues relating to influenza in	Noted. See above

Comment from	Nature of comment	Response
	individuals with major immunosuppression.	
British Thoracic Society	*Are there any equality related issues that may need special consideration?* The definition of an influenza outbreak differs between in England and Wales which may result in regional differences in the use of oseltamivir, and zanamivir for the prophylaxis of influenza.	Noted.
Diabetes UK	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Diabetes UK questions the interpretation of the clinical and cost effectiveness evidence that has resulted in a recommendation that these technologies are not made available for seasonal prophylaxis (1.7). The decision to limit use of these technologies to post exposure prophylaxis appears to be based primarily on reasons of cost effectiveness. The Committee state in 4.3.5 that the "drugs were clinically effective when used as seasonal or post exposure prophylaxis". The Committee also acknowledges that the economic modelling for cost effectiveness was weak owing to the lack of available evidence, therefore in many instances evidence in the healthy adult populations was used to make assessments for the at risk populations. Furthermore in at risk, unvaccinated, children seasonal prophylaxis was found to be cost effective although consideration was given to issues with some of the data (4.3.8).	
Diabetes UK	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** **1.2** As outlined previously Diabetes UK particularly welcomes recommendation 1.2 that emphasises that decisions as to which technology is used are based on discussion and consider issues such as preference regarding delivery, potential adverse effects	Noted

Comment from	Nature of comment	Response
	and contraindications. **1.7** Diabetes UK recommends that these technologies are also made available for seasonal prophylaxis. The decision to limit use of these technologies to post exposure prophylaxis appears to be based primarily on reasons of cost effectiveness as outlined above. If seasonal prophylaxis is not available it potentially places people, particularly from at risk populations such as people with diabetes, at increased risk of catching influenza in circumstances where there is a mismatch between the vaccine and the circulating influenza virus, or where the flu vaccination is contraindicated for use in an individual. Where this is the case, for some individuals, it may be too late to instigate post exposure prophylaxis as the individual may not attend at their GP surgery in time to have the necessary tests undertaken that would inform whether or not the individual can have a particular technology. **1.8** The Committee has decided not to recommend amantadine having considered the evidence surrounding the adverse effects, the age of the trials and the level of resistance the influenza virus has developed in relation to this technology. Diabetes UK is mindful of the concerns outlined above and would encourage NICE to review their position in the future in light of any further evidence or research made available. Provided it is safe and effective, and the necessary screening for contraindications has been undertaken, this technology could be an option for prophylaxis in instances where either the flu vaccination or the other technologies considered in this appraisal are inappropriate or contraindicated.	In the situation of a mismatch between vaccine and circulating virus strains or when vaccination is contraindicated, at-risk people are eligible for PEP. (See FAD 1.5) The Committee noted limited evidence of the clinical effectiveness of amantadine, evidence of side-effects and resistance to amantadine, and did not find this a cost-effective option and did not recommend its use as prophylaxis. (see sections 4.3.6 and 4.3.14 of the FAD).

Comment from	Nature of comment	Response
Diabetes UK	**Are there any equality related issues that may need special consideration? 1.6** This recommendation must also consider the needs of populations residing in institutions such as prisons. People from at risk populations residing in these institutions must also have their needs considered. The recommendation as it currently stands does not explicitly include these populations.	For the Committee's considerations of post-exposure prophylaxis in prisons during an outbreak - please see section 4.3.13 of the FAD.
Diabetes UK	**General** Enabling and supporting timely access to these technologies for people without a fixed address must also be considered to ensure people from these populations are not put at increased risk of catching influenza.	People without a fixed address were not considered as a separate subgroup. Should such a person fall within the recommendations set out in sections 1.1 to 1.5 of the FAD, post-exposure prophylaxis would be recommended.
GPIAG	Our first comment is that this guidance needs to be more clearly labelled as relating to post exposure prophylaxis. There has been confusion with NICE doing the two appraisals for treatment and prophylaxis simultaneously and it is important that the prophylaxis context of this appraisal is unambiguous. There is a danger that GPs/ nurses may not appreciate the significance of this guidance when it lands on their desks. Lack of familiarity with the medicines may also mean that many patients and health professionals are not aware of the marketing authorisation that the drugs need to be given within 48 hours of exposure. It would be good to spell out this 48 hour rule	The guidance related to both PEP and seasonal prophylaxis. The FAD has been amended to specify that the drugs need to be given within a specified time of exposure (FAD 1.1)

Comment from	Nature of comment	Response
	in para 1.1.	
GPIAG	In broad terms we feel that the guidance is clear. There are a few issues that we think require clarification however. We have several questions about the groups that qualify as 'at risk'. There is no mention of carers in this context, yet we consider them to be key to protect if they have responsibility for others. Healthcare workers are also not mentioned, yet they are often exposed to infection early on in an outbreak. At present, they would appear to be ineligible according to the guidance. Are these exclusions intentional?	No evidence for cost-effectiveness specifically in carers or healthcare professionals was placed before the Committee. The Committee did not make specific recommendations for post-exposure prophylaxis for healthcare workers or carers - the general recommendations in section 1 apply to these groups.
GPIAG	There is no reference here to use of the products in an Out of Hours (OOH) context, immediately post-exposure. In this situation the clinician will have no access to patient records or knowledge of the patient's history. It may be that an OOH doctor should err on the side of initiating treatment prophylactically for example. We believe that guidance about what to do in this context would be useful. In a different scenario, arrangements for the use of these drugs in a residential home with an outbreak of influenza over the Bank Holiday Weekend need to be in place. It is not reasonable to expect a Duty Doctor or other health care professional to turn up and find him- or herself in the position of being expected to deal with that. PCTs ought to make positive arrangements for that with their OOH providers, perhaps using Patient Group Directions. Some reference to clarify OOH situations would therefore be useful.	This Technology Appraisal Guidance has been developed within the remit to appraise the clinical and cost effectiveness of the technologies within their licensed indications. Technology Appraisal guidance does not cover every possible eventuality when influenza prophylaxis

Comment from	Nature of comment	Response
		would be considered.
GPIAG	1.7 - Would it make more sense to make the point that the treatments are not to be used for seasonal prophylaxis immediately after point 1.1 rather than as point 1.7? It would also be good to give a definition of seasonal versus post –exposure prophylaxis.	The definitions for prophylaxis are within the FAD. See 2.7
GPIAG	Occupational health departments should be considered here. They could be a very effective place to initiate prophylactic treatment, if there are known cases of flu in a workforce. It appears that you are only considering exposure within the home environment, whereas people may be exposed at work too (as in the case of healthcare professionals, as above). Again, some specific comments on this situation would be useful.	The Committee considered that the intensity of exposure would have to be of the degree of that experienced by 'living together in then same residential setting' for prophylaxis to be considered cost-effective (see FAD 4.3.11).
GPIAG	Publicity of the threshold levels of circulating influenza needs to be clear. It is published, and it was actually picked up in the media this year, but as it is a central element of the indications for the use of these drugs PCTs should consider how that information is to be circulated to GPs. What we feel is very unclear is how the products should be used in the case of influenza outbreak or pandemic. While the guidance does not seek to cover these situations, there should be some indication if/where such guidance can be obtained.	See above – the recommendations do not cover the occurrence of a pandemic and this is stated in the guidance section.
HPA	*Do you consider that all of the relevant evidence has been taken into account?* Appendix B: Apart from input from the Health Protection Agency, there appears to have been no formal input from the microbiology/virology/infectious disease specialty groups.	Noted
HPA	*Do you consider that the provisional recommendations of the Appraisal Committee*	The FAD has been

Comment from	Nature of comment	Response
	are sound and constitute a suitable basis for the preparation of guidance to the NHS? Page 3, Section 1.1, 4th bullet and throughout the document (see also page 26, Section 4.3.4): It is somewhat misleading to state that the surveillance scheme threshold is used to determine "whether influenza virus is circulating in the community." The threshold demarcates (as correctly stated in Section 1.6, page 5) "normal seasonal activity." However, when the GP consultation rate falls below this level, there are other data (as detailed in the HPA Weekly National Influenza Report) that clearly indicate that the influenza virus is "circulating in the community."	amended to take note that the threshold for the surveillance scheme indicates 'normal seasonal activity'. See sections 1.1 including footnote, 1.6, 4.1.14, and 4.3.3 to 4.3.5.

Comment from	Nature of comment	Response
HPA	The NICE document suggests that no alternative method was proposed for determining whether influenza virus was circulating in the community. This is not the case. The HPA view, and supported by the recent action by the NPHS Wales (which re-issued, on behalf of the Welsh Assembly Government, the recommendation to use anti-virals in the light of the circulation of influenza B late in this season), is that the national health protection bodies in England, Wales, Scotland and Northern Ireland should determine whether or not influenza virus is circulating in the community based on their range of surveillance indicators. Although it would be convenient and administratively simpler if there were a routinely available single numerical indicator to indicate reliably the circulation of influenza viruses in the community, no such single indicator exists. The advice to the respective Health Departments, to advise practitioners on whether the period when it was appropriate to prescribe influenza antivirals had arrived, should be provided by the health protection bodies conducting the influenza surveillance.	The FAD has been amended. See sections 1.1 including footnote, 1.6, 4.1.14, and 4.3.3 to 4.3.5.
HPA	Page 26, Section 4.3.4. Strong consideration should be given to replacing “whether influenza virus is circulating” with “normal seasonal activity.”	FAD amended
HPA	Page 4, Section 1.3: Not included in this list are other groups for whom vaccination is recommended, such as health care workers and caregivers of persons at risk. In certain situations, might post-exposure prophylaxis be considered; for example, an unvaccinated health care worker or caregiver of a person at risk who is a close contact of a person with influenza?	The Committee did not make specific recommendations for post-exposure prophylaxis for healthcare workers or carers - the general recommendations in section 1 apply to these groups. No estimates for cost-effectiveness in these subgroups were presented.

Comment from	Nature of comment	Response
HPA	Page 4, Section 1.5: Persons at risk who were vaccinated after circulation of influenza virus has begun may not be effectively protected for at least 2 weeks or more and should be considered for inclusion in this group.	Please see FAD 1.5, second bullet.
HPA	Page 4, Section 1.4: Close contact might reasonably be expected to occur in closed settings other than households, such as residential institutions, boarding schools, and the like. Depending on the nature of the prevalent influenza illness, there may be strong public health reasons to extend prophylaxis to other residential groups. A virus, for example, causing particularly severe disease in children might prompt a greater level of protective action in a boarding school outbreak. As written, it appears overly restrictive.	Section 1.4 of the FAD has been amended to include 'or residential setting'. The Committee considered that prophylaxis was only cost-effective out of season in closed settings where a majority of people in such residential care were ‘at-risk’ individuals (see FAD 4.3.13).
HPA	Page 5, Section 1.6: Only residential and nursing homes are cited; similar to the comment for Section 1.4, this may be too restrictive and importantly excludes other closed settings such as prisons as well as hospital settings where nosocomial transmission has been well documented.	See above.
HPA	Page 25, Section 4.3.2: As noted above, the at-risk groups are not defined exactly as they are for current vaccine recommendations.	Noted. The FAD has been amended.
HPA	Page 31, Section 4.3.11: Use of antivirals for outbreak settings is sensible, but consideration should be given to making language somewhat less restrictive (similar to previous comments) as there may be setting other than “long-term residential or nursing homes” where prophylaxis would be appropriate.	Noted. The Committee considered the setting and its conclusions are in section 4.3.13 of the FAD
RCPCH	The document appears to be comprehensive, and the interpretations and recommendations appear reasonable. However, without a full reference list it is hard to be certain all the evidence has been appraised.	Noted. Reference lists can be found in the Assessment Report and in submissions

Comment from	Nature of comment	Response
		from manufacturers and consultees.
RCPCH	What is completely lacking is any recommendation (either clinical or research) about young children; particularly infants <12 months of age for whom there is no neuraminidase licensed, and children who are unable to take oral or inhaled medication. Although this appraisal is for prophylaxis with antiviral agents, for those in whom none of the agents in question is either licensed or appropriate, alternative recommendations should be made available (i.e. ensuring that appropriate vaccination advice is followed for risk groups, or ensuring that a research recommendation for alternatives for these groups are actively sought).	Guidance is issued within the referred remit to appraise the technologies within their licensed indications.
RCPCH	For infants there are published data on oseltamivir to support further research. The RCPCH is disappointed that where specific trials of drugs in children have taken place (as in 4.1.1 and 4.1.10) the findings relative to children have not been detailed.	Comment noted. Evidence is summarised in the FAD. Further details can be found in the submitted evidence.
RCPCH	The RCPCH also recommend a research recommendation is made regarding alternative methods of administering zanamivir so that it can be administered to younger children (<5 years).	Comment noted. See section 6 of FAD. Technologies are appraised within their licensed indications.
RCN	Nurses working in this area of health have reviewed the Appraisal Consultation Document. The document is comprehensive. The Royal College of Nursing would welcome guidance to the NHS on the use of these health technologies for the prophylaxis of influenza.	Noted
RCP	Please take this e-mail as confirmation that the Royal College of Physicians wishes to endorse the response on the ACD put forward by the BTS.	Noted
DoH	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Noted

Comment from	Nature of comment	Response
WAG	We are particularly encouraged by the move to recognise the value of antivirals even when the evidence of flu circulating nationally may not be there. This accords with our recent experience in Wales of Influenza B outbreaks, which if we had followed the NICE guidelines currently in existence, might have reduced our likelihood of using the antivirals. Otherwise, we are content with the technical detail of the evidence supporting the appraisal however it would be desirable to see even less emphasis on the requirements around a trigger and much more use of clinical judgement as we normally see with other anti-microbials, i.e. antibiotics for bacteria.	Comments noted
Web Comments NHS Professional	I work in an acute trust where we are expected both to comply and to demonstrate compliance with NICE guidance. I have always used the existing version of this guideline to illustrate how we are expected to do the impossible. The audit suggestions were basically to look at those given prophylaxis to ensure they met the criteria, and to look at those who met the criteria to ensure they received prophylaxis. The former is easy, particularly in an organisation like this where nobody has received these drugs in any of the previous four or five flu seasons. I can assure the trust, and NICE, that nobody has been inappropriately prescribed flu prophylaxis. However from a clinical perspective it is much more important to address whether people who met the criteria received prophylaxis, but this is impossible within any conceivable resource constraints, either retrospectively (since ILI exposure and many of the risk groups are not retrievable from clinical coding) or prospectively (since there is no single place at which the decision might be made, and it is impractical to try to engage all areas in such an audit). I think you should accept that this question is not auditable.	Comments noted. These comments will be sent to the NICE Implementation directorate which oversees the development of audit criteria.