NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA158; Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of TA67)

This guidance was issued in September 2008.

The review date for this guidance is September 2011.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal. That we add to the NICE TA158 webpage the hyperlink to the current Chief Medical Officer advice on influenza.

Original remit(s)

To review the Institute's earlier advice on the clinical and cost-effectiveness of amantadine and oseltamivir, and to advise on the clinical and cost effectiveness of zanamivir, in their licensed indications for the prevention of influenza A and B, both relative to one another and to best symptomatic care.

Current guidance

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no community resistance.

1.1 Oseltamivir and zanamivir are recommended, within their marketing authorisations, for the post-exposure prophylaxis of influenza if all of the following circumstances apply.

- National surveillance schemes have indicated that influenza virus is circulating[1].
- The person is in an at-risk group as defined in section 1.3.
- The person has been exposed (as defined in section 1.4) to an influenza-like illness and is able to begin prophylaxis within the timescale specified in the marketing authorisations of the individual drugs (within 36 hours of contact

[1] The Health Protection Agency in England (and the equivalent bodies in Wales and Northern Ireland) uses information from a range of clinical, virological and epidemiological influenza surveillance schemes to identify periods when there is a substantial likelihood that people presenting with an influenza-like illness are infected with influenza virus.

with an index case for zanamivir and within 48 hours of contact with an index case for oseltamivir).

• The person has not been effectively protected by vaccination (as defined in section 1.5).

1.2 The choice of either oseltamivir or zanamivir in the circumstances described in section 1.1 should be determined by the healthcare professional in consultation with patients and carers. The decision should take into account preferences regarding the delivery of the drug and potential adverse effects and contraindications. If all other considerations are equal, the drug with the lower acquisition cost should be used.

1.3 For the purpose of this guidance, people at risk are defined as those who fall into one or more of the clinical risk groups defined, and updated, each year by the Chief Medical Officer. The current list includes people with:

• chronic respiratory disease (including asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission)

• chronic heart disease

• chronic renal disease

• chronic liver disease

• chronic neurological disease

• immunosuppression

• diabetes mellitus.

People who are aged 65 years or older are also defined as at-risk for the purpose of this guidance.

1.4 Exposure to an influenza-like illness is defined as close contact with a person in the same household or residential setting who has had recent symptoms of influenza.

1.5 People who are not effectively protected by vaccination include:

• those who have not been vaccinated since the previous influenza season

• those for whom vaccination is contraindicated, or in whom it has yet to take effect

• those who have been vaccinated with a vaccine that is not well matched (according to information from the Health Protection Agency) to the circulating strain of influenza virus.

1.6 During localised outbreaks of influenza-like illness (outside the periods when national surveillance indicates that influenza virus is circulating generally in the

community), oseltamivir and zanamivir may be used for post-exposure prophylaxis in at-risk people living in long-term residential or nursing homes, whether or not they are vaccinated. However, this should be done only if there is a high level of certainty that the causative agent in a localised outbreak is influenza, usually based on virological evidence of infection with influenza in the index case or cases.

1.7 Oseltamivir and zanamivir are not recommended for seasonal prophylaxis of influenza.

1.8 Amantadine is not recommended for the prophylaxis of influenza.

2. Rationale[2]

The new clinical evidence that has been published since TA158 was issued is consistent with the conclusions by the Appraisal Committee on the clinical effectiveness of oseltamivir and zanamivir. There have been no relevant changes to the price of oseltamivir, zanamivir or amantadine, and no information is available about any changes to the marketing authorisation or any relevant new or ongoing trials of the effectiveness of these drugs. Based on this information it is proposed that the guidance is placed on the static list.

3. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal.

4. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2007 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5. Summary of evidence and implications for review

Roche, the manufacturer of oseltamivir has no plans to extend the marketing authorisation of oseltamivir for influenza prophylaxis and did not identify any recent relevant studies. Alliance Pharmaceuticals, the manufacturer of amantadine did not respond to the request for information about their marketing authorisations and about the availability of new evidence. GlaxoSmithKline currently has no plans to extend the marketing authorisation for zanamivir. GlaxoSmithKline identified a limited number of publications referencing zanamivir for prophylactic use since the last NICE Technology appraisal in 2008.

[2] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

Since the publication of TA158 (September 2008), the marketing authorisations for zanamivir, oseltamivir, and amantadine have not changed. The price for zanamivir has not changed, while the price for oseltamivir has decreased from £16.36 to £15.41. The price for amantadine has increased from £4.80 to £5.76 for 14 capsules (100 mg each), while the price for 5 capsules has remained at £2.40.

The updated literature search identified two ongoing and five completed studies related to influenza prophylaxis with oseltamivir or zanamivir. One ongoing study (NCT01286142 [expected date of completion May 2012] and one completed study (NCT00391768 [completion date: March 2010]) appear to address the Committee's research question regarding the development of options for influenza prophylaxis in infants 12 months of age or younger. The other ongoing study (NCT01053377 [expected date of completion December 2013] is a randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes.

The unpublished results of two post-marketing observational studies on the efficacy and safety of the prophylactic use of zanamivir (NCT01156701 and NCT01390792) showed a consistent protective efficacy against influenza. Another unpublished RCT (NCT00412737 [completed November 2008]) evaluated the efficacy and safety of oseltamivir in the seasonal prophylaxis of influenza in immunocompromised patients, but did not reach its primary endpoint.

Some of these studies were conducted in young children and infants, possibly addressing the research recommendations made in TA158. However, the manufacturers have not expressed any intention on seeking extensions to their current EU marketing authorisations based on these studies (oseltamivir already has marketing authorisation for all ages and zanamivir is licensed for ages 5 and older).

Some of the trials identified studied the efficacy of these drugs in pandemic situations. However, the use of oseltamivir and zanamivir in a pandemic situation is outside the scope of the original appraisal. Additionally, the Chief Medical Officer has identified additional 'at-risk' groups since 2010 (DH, April 2011, Explanatory memorandum to the National Health Service 2011 No. 680). This is consistent with the current guidance, which states that people at risk are defined as those who fall into one or more of the clinical risk groups defined, and updated, each year by the Chief Medical Officer. As a result, because there is no new relevant evidence that would lead to a change to the current NICE recommendations at this time, it would be appropriate for this guidance to be transferred to the 'static guidance list'.

Because guidance section 1.3 refers to the clinical risk groups defined, and updated, each year by the Chief Medical Officer, we suggest that we add to the web page of TA158 a hyperlink to the current advice from the Chief Medical Officer, with the following text:

"Guidance section 1.3 refers to the fact that the clinical risk groups are defined and updated each year by the Chief Medical Officer. For more information please see Annex C in the 2011/12 Seasonal flu plan:

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_127088.pdf "

6. Implementation

A submission from Implementation is included in Appendix 3.

The implementation advice suggests that oseltamivir and zanamivir both increased in use after TA158 was published as expected. However, the increase in zanamivir usage has been modest compared with oseltamivir. This may be explained by the difference in price. The HPA in its recent guidance “Pharmacological treatment and prophylaxis of influenza” (Jan 11) state that although either drug is considered clinically adequate, oseltamivir is preferred because of its wider availability through community pharmacy outlets.

7. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: Elisabeth George, 30 08 11

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below.

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

TA168 Amantadine, oseltamivir and zanamivir for the treatment of influenza (review of existing guidance No. 58). Published February 2009, review date November 2013.

In progress

None found

Suspended/terminated

None found

In topic selection[3]

None found

[3] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
Oseltamivir (Tamiflu, Roche) is a neuraminidase inhibitor that is active against influenza A and B viruses For post-exposure prophylaxis, oseltamivir should be started within 48 hours of contact with an index case of influenza-like illness and continued for 10 days. For seasonal prophylaxis, oseltamivir is given for up to 6 weeks. Oseltamivir costs £16.36 for a 10-day course for an adult (excluding VAT; 'British national formulary' [BNF] edition 54).	From eBNF (edition 61): Unchanged, but with the additional information: "Data on the use of oseltamivir in children under 1 year of age is limited. Furthermore oseltamivir may be ineffective in neonates because they may not be able to metabolise oseltamivir to its active form. In exceptional circumstances, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age." "There is evidence that some strains of influenza A virus have reduced susceptibility to oseltamivir, but may retain susceptibility to zanamivir." According to eMC "The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks." The net price in eBNF 61 for a 10 day course for an adult is £15.41

Indication considered in original appraisal	Proposed indication (for this appraisal)
Zanamivir (Relenza, GlaxoSmithKline) is a neuraminidase inhibitor that is active against influenza A and B viruses...It has a marketing authorisation for post-exposure prophylaxis of influenza A and B in adults and children (5 years and older) following contact with a clinically diagnosed case in a household. In exceptional circumstances, zanamivir may be considered for seasonal prophylaxis of influenza A and B (for example, during a community outbreak in the case of a mismatch between circulating and vaccine strains, and in a pandemic situation). For post-exposure prophylaxis zanamivir should be initiated within 36 hours of contact with an index case of influenza-like illness and continued for 10 days. For seasonal prophylaxis, zanamivir is given for up to 28 days. Zanamivir is administered by oral inhalation using an inhaler device. The price of zanamivir was reduced during the course of the appraisal to £16.36 for a 10-day course. The price of zanamivir currently listed in the BNF is £24.55 for a 10-day course (excluding VAT; BNF edition 54).	From eBNF (edition 61): Unchanged. The net price listed is £16.36

Indication considered in original appraisal	Proposed indication (for this appraisal)
Amantadine (Lysovir, Symmetrel, Alliance Pharmaceuticals) acts against influenza A virus by blocking viral replication. The marketing authorisation recommends amantadine prophylactically in people particularly at risk. This can include those with chronic respiratory disease or debilitating conditions, the elderly and those living in crowded conditions. It can also be used for members of families in which influenza has already been diagnosed, for control of institutional outbreaks or for those in essential services who are unvaccinated or when vaccination is unavailable or contraindicated. It is also recommended as post-exposure prophylaxis in conjunction with inactivated vaccine during an outbreak until protective antibodies develop, or in people who are not expected to have a substantial antibody response (because of immunosuppression). Amantadine is licensed for use in people aged 10 years or older. The SPC states that treatment is recommended for as long as protection from infection is required and that in most instances this is expected to be for 6 weeks. In clinical practice this corresponds to its use as seasonal prophylaxis. For post-exposure prophylaxis, amantadine is usually given for 4–5 days Amantadine costs £2.40 for five capsules (100 mg each), £4.80 for 14 capsules and £5.55 for 150 ml syrup (50 mg/5 ml) (excluding VAT; BNF edition 54).	From eBNF (edition 61): “Amantadine is licensed for prophylaxis and treatment of influenza A but it is no longer recommended (see NICE guidance).” For prophylaxis, eBNF 61 says the dose for adults and children aged 10 years or over is “100 mg daily usually for 6 weeks or with influenza vaccination for 2–3 weeks after vaccination.” This is the same as the eMC entry. eMC makes no mention of 4 – 5 days. The dose of 4 – 5 days corresponds in eBNF to the treatment of influenza with amantadine. For capsules: eBNF 61 lists the cost as “100 mg, net price 5-cap pack = £2.40, 14-cap pack = £5.76” For syrup: eBNF 61 lists the cost as “50 mg/5 mL. Net price 150-mL pack = £5.33.”

Details of new products

None for prophylaxis apart from pandemic vaccine technologies

Registered and unpublished trials

Trial name and registration number	Details
NCT01053377 A randomised controlled trial on the effect of post-exposure Oseltamivir prophylaxis on influenza transmission in nursing homes	Phase IV post-exposition prophylaxis with oseltamivir or placebo. Enrolling by invitation. Estimated enrolment: 900 Estimated study completion date: December 2013 Estimated primary completion date: December 2013
NCT00391768 Oseltamivir Treatment for Children Less Than 24 Months of Age With Influenza	A completed pharmacokinetic/ pharmacodynamic and safety evaluation of oseltamivir for the treatment of children less than 24 months of age with confirmed influenza infection. Results available. Enrolment: 87 Primary completion date: March 2010
NCT01156701 Prophylactic efficacy of Relenza against Influenza A and B	Post-marketing observational study to assess the efficacy of Relenza when used as prophylaxis against influenza (study completed, results not found in the published literature but a conference proceeding abstract is available and GSK has supplied a report) Enrolment: 171705 Primary completion date May 2010
NCT00412737 A double-blind, randomized, placebo controlled, multi-centre trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients	Phase IV, completed 2008 but unpublished. A report is available via the Roche website.

Trial name and registration number	Details
NCT01390792 Special drug use investigation for Relenza® (zanamivir) (prophylaxis)	A completed (2009) post marketing observational study, for the Japanese Pharmaceuticals and Medical Devices Agency. GSK has supplied a report of the results.
NCT01286142 A prospective, observational safety study in children <= 24 months of age receiving Oseltamivir for the treatment or prophylaxis of influenza infection Relates to the research recommendation: 6.2 Research is required to develop options for prophylaxis of influenza in infants (under 12 months of age).	Ongoing, not recruiting. Primary completion date: July 2010 Estimated enrolment: 900 Estimated study completion date: May 2012 Preliminary reports or results were not found in the published literature, or via the Roche website.

References

Department of Health, Explanatory memorandum to the National Health Service (General Medical Services Contracts) (Prescription of drugs etc.) (Amendment) regulations 2011 no. 680.

Appendix 3 – Implementation submission

Implementation feedback - review of technology appraisals: report for guidance executive

Technology Appraisal	**TA158 Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza**
Implementation input required by date	**11/07/2011**

1. Routine healthcare activity data

1.1 Primary care and hospital outpatient prescribing (ePACT and hospital ePACT) - oseltamivir, amantadine and zanamivir

This section provides information on cost and volume of oseltamivir, amantadine and zanamivir prescribed and dispensed in primary care in England using data obtained from the electronic Prescribing Analysis and Cost Tool (ePACT) system. Cost and volume data on hospital outpatient prescriptions was obtained from hospital ePACT. ePACT and hospital ePACT data is only available from April 2009 to April 2011, however technology appraisal 158 was published in September 2008. All costs stated in this report are based on Net Ingredient Cost (NIC).

Figure 1 below shows prescribing costs for amantadine, oseltamivir and zanamivir in primary care and hospital outpatients combined. Costs for all three drugs remained consistently low from February 2010 until November 2010. Costs of oseltamivir increased to £300,556.44 during January 2011, whilst costs for amantadine and zanamivir remained low. TA158 was published in September 2008; however it is unclear as to whether there was a similar effect in the previous year as prescribing data from ePACT and hospital ePACT is currently unavailable prior to April 2009.

Figure 1 Trend in cost of prescribing oseltamivir, amantadine and zanamivir in primary care and hospital outpatients in England

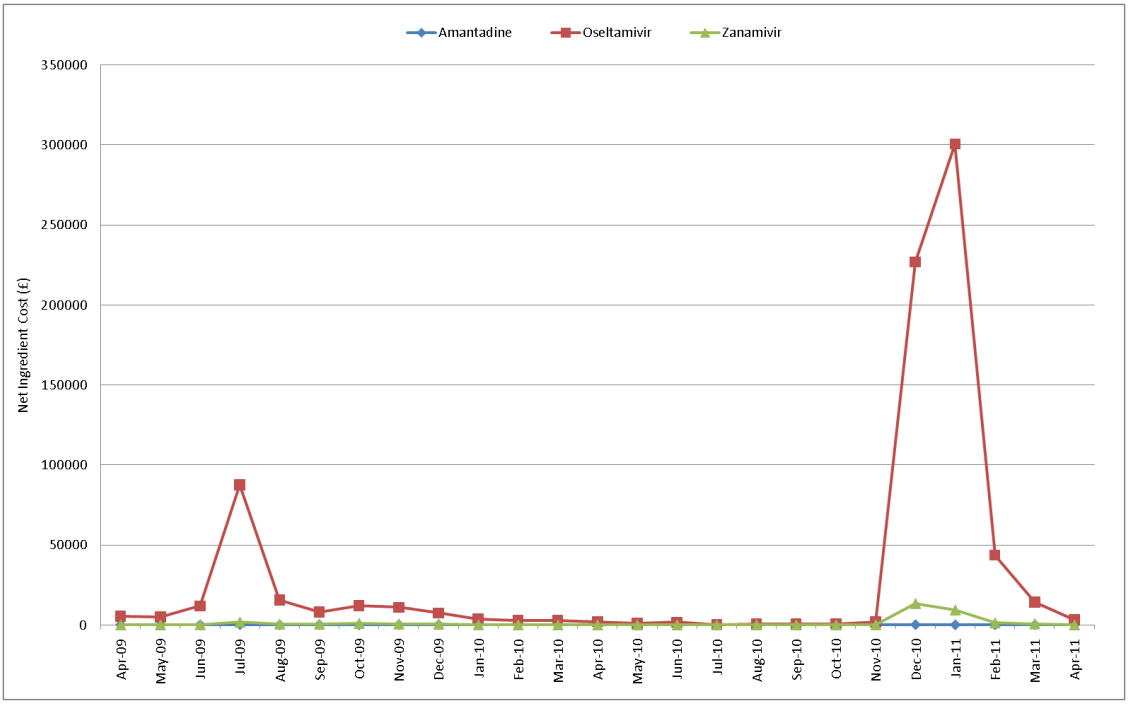
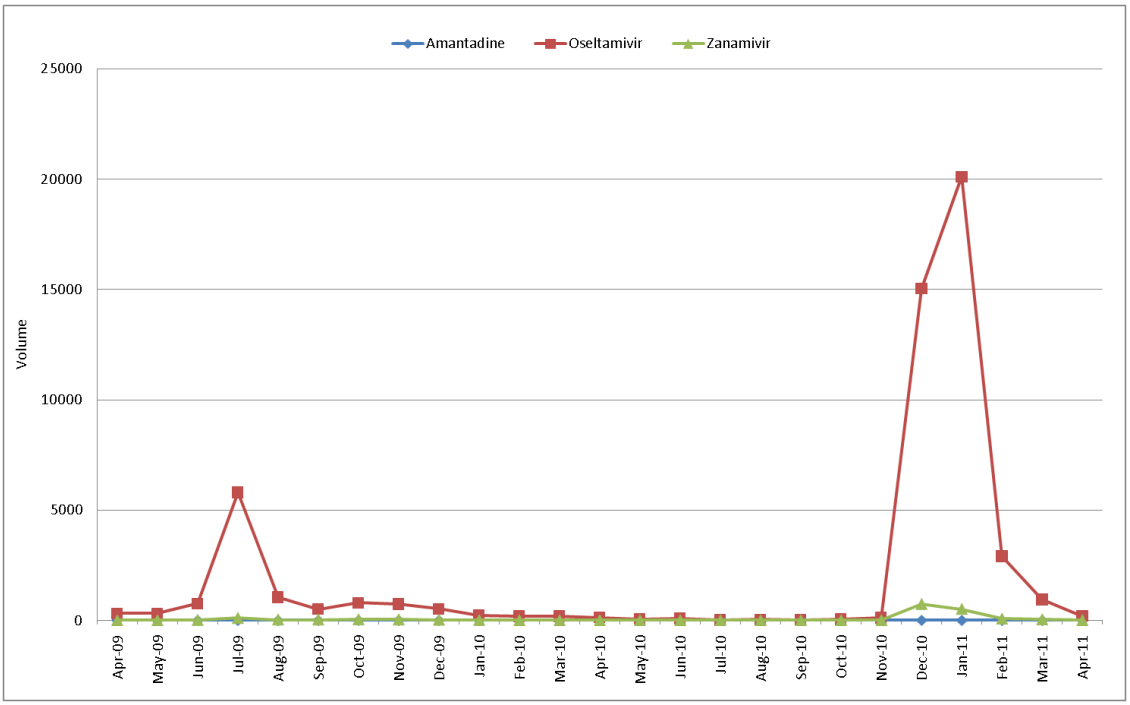


Figure 2 below shows prescribing volume of amantadine, oseltamivir and zanamivir in primary care and hospital outpatients combined. The volume of all three drugs remained consistently low from February 2010 until November 2010. Volume of oseltamivir increased to 20,000 prescription items during January 2011, whilst volume of amantadine and zanamivir remained low. TA158 was published in September 2008; however it is unclear as to whether there was a similar effect in the previous year as prescribing data from ePACT and hospital ePACT is currently unavailable prior to April 2009.

Figure 2 Trend in volume of prescribing oseltamivir, amantadine and zanamivir in primary care and hospital outpatients in England



1.2 Hospital pharmacy audit prescribing (HPAI) – oseltamivir, amantadine and zanamivir

Data showing trends in prescribing costs and volume from hospital pharmacies are presented below in figures 3 and 4. There is a sharp increase in cost and volume of oseltamivir after the publication of TA158. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Figure 3 Trend in volume of prescribing oseltamivir, amantadine and zanamivir in hospital pharmacies in England

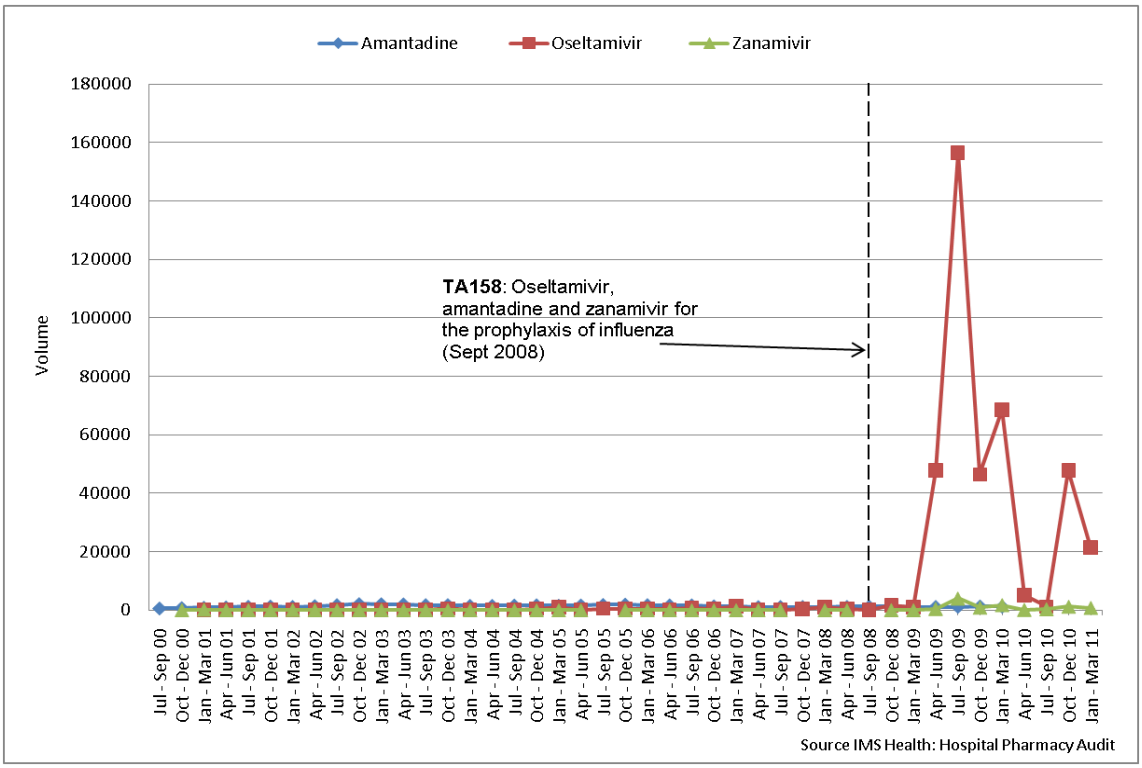
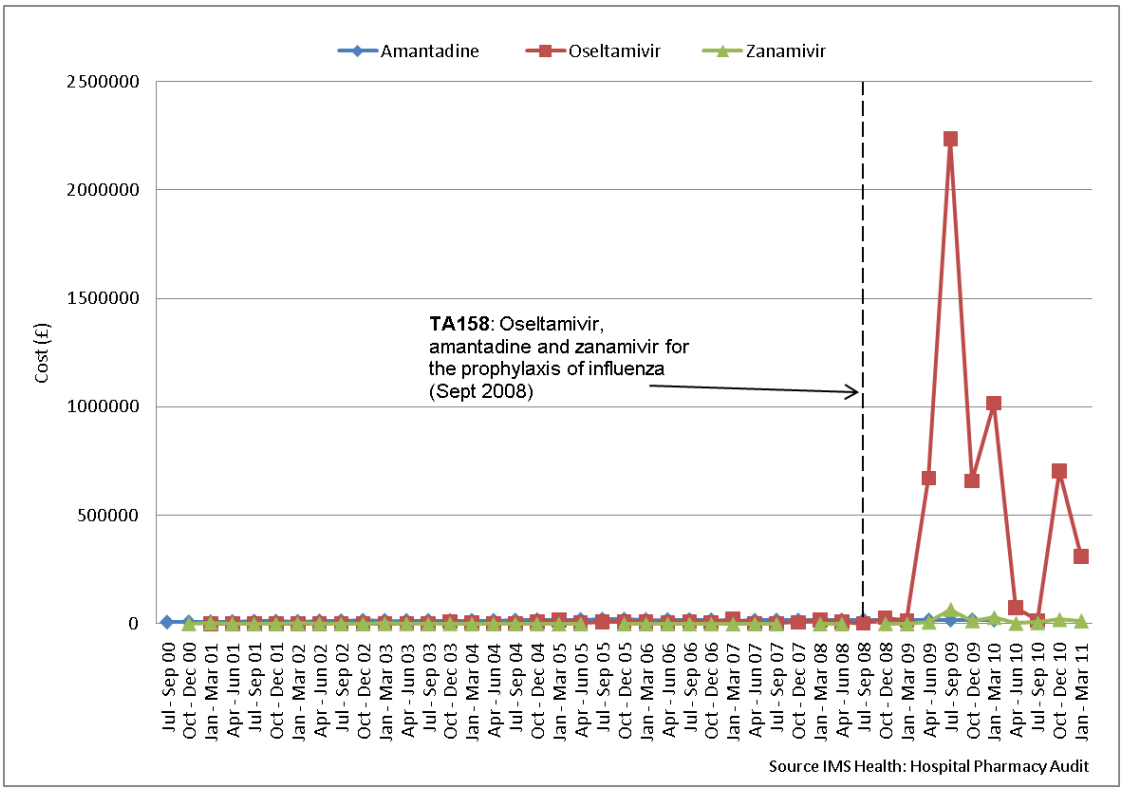


Figure 4 Trend in cost of prescribing oseltamivir, amantadine and zanamivir in hospital pharmacies in England



2. Implementation studies from published literature

Information is taken from the ERNIE website

Nothing to add at this time.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Nothing to add at this time.