The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 November 2011

TAMIFLU 12 mg/ml, powder for oral suspension
1 vial of 30 g (CIP code: 359 963-5)
TAMIFLU 75 mg, capsule
B/10 (CIP code: 359 962-9)
TAMIFLU 45 mg, capsule
B/10 (CIP code: 382 016-9)
TAMIFLU 30 mg, capsule
B/10 (CIP code: 382 015-2)

Applicant: ROCHE

Oseltamivir phosphate
ATC code: J05AH02

List I

Date of Marketing Authorisation (centralised European procedure):
TAMIFLU 12 mg/ml, powder for oral suspension and 75 mg capsule: 20/06/2002
TAMIFLU 30 mg and 45 mg capsule: 19 September 2007
Extension of indication to children under 12 months of age during an influenza pandemic: 23 October 2009

Reason for request:
- Re-assessment of the actual benefit (AB) as a curative influenza treatment during periods of virus circulation and during an influenza pandemic in accordance with article R 163-12 of the Social Security Code.
- Extension of indication to children less than 1 year of age during an influenza pandemic outbreak as curative and prophylactic treatment of influenza.

Medical, Economic and Public Health Assessment Division
### Previous assessments from the Transparency Committee: AB, IAB

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<td><strong>Inclusion request</strong></td>
<td><strong>Opinion dated 11 February 2004</strong></td>
<td><strong>Opinion dated 21 June 2006</strong></td>
<td><strong>Opinion dated 3 January 2007</strong></td>
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<td><strong>Opinion dated 11 February 2004</strong></td>
<td><strong>Submission of new studies:</strong> preventative in children (extension of indication) + curative</td>
<td><strong>Confirmation of insufficient AB in all situations from 12 months of age</strong></td>
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<td><strong>Post-contact prophylaxis</strong></td>
<td><strong>Insufficient AB in the adolescent and adult without comorbidity</strong></td>
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<td><strong>Insufficient AB in the adolescent and adult without comorbidity</strong></td>
<td><strong>Low AB in the adolescent and adult with comorbidity and in subjects over 65 years of age</strong></td>
<td><strong>Low AB in children with comorbidity</strong></td>
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<tr>
<td><strong>Low AB in the adolescent and adult with comorbidity and in subjects over 65 years of age in particular situations:</strong></td>
<td><strong>Moderate AB in the adolescent and adult with comorbidity in particular situations:</strong></td>
<td><strong>Moderate AB in children with comorbidity in particular situations:</strong></td>
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<tr>
<td>- institutionalised patients, contraindication to the vaccine, immunocompromised subjects, incomplete vaccine protection compared to the circulating strain.</td>
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<tr>
<td><strong>IAB V in the management of post-exposure prophylaxis children from 1 to 12 years</strong></td>
<td><strong>IAB III relative to Mantadix</strong></td>
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<tr>
<td><strong>Exceptional situation</strong></td>
<td><strong>Substantial AB (conditional) in the seasonal prophylaxis in an exceptional situation:</strong> epidemic situation with mismatch between the vaccine and circulating strains, pandemic situation</td>
<td><strong>Insufficient AB in children and adults without comorbidity</strong></td>
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<tr>
<td><strong>Insufficient AB in children and adults without comorbidity</strong></td>
<td><strong>Low AB in the following high-risk patients:</strong> children over 1 year of age with comorbidity, adults from 13 to 64 years of age with comorbidity and adults over 65 years of age.</td>
<td><strong>Moderate AB in the particular case of at-risk subjects:</strong></td>
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<td>- subjects living in institutions (institutionalised patients)</td>
<td><strong>Moderate AB in the particular case of at-risk subjects:</strong></td>
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<td>- subjects with contraindication to the vaccine</td>
<td><strong>Insufficient AB in children and adults without comorbidity</strong></td>
<td><strong>Low AB in the following high-risk patients:</strong> children over 1 year of age with comorbidity, adults from 13 to 64 years of age with comorbidity and adults over 65 years of age.</td>
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<td>- immunocompromised subjects (in particular AIDS subjects, transplant recipients or patients receiving immunosuppressive drugs)</td>
<td><strong>Moderate AB in the particular case of at-risk subjects:</strong></td>
<td><strong>Insufficient AB in children and adults without comorbidity</strong></td>
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<tr>
<td>- situations in which the vaccine only provides limited protection against the circulating strain</td>
<td><strong>Moderate AB in the particular case of at-risk subjects:</strong></td>
<td><strong>Insufficient AB in children and adults without comorbidity</strong></td>
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</table>
| TC assessment | Opinion dated 16 April 2008  
Re-assessment of the AB at the request of 
the Ministry of Health  
COSMOS observational study + other data provided | Opinion dated 21 October 2009  
Re-inclusion  
Submission of six new studies |
| Curative treatment | Confirmation of **insufficient** AB in all situations from 12 months age | Confirmation of **insufficient** AB in all situations from 12 months of age |
| Post-contact prophylaxis | **Insufficient** AB in children and adults without comorbidity  
**Low** AB in the following high-risk populations:  
children over 1 year of age with comorbidity,  
adults from 13 to 64 years of age with comorbidity and adults over 65 years of age.  
**Moderate** AB in the particular case of at-risk subjects:  
- subjects living in institutions (institutionalised patients)  
- subjects with contraindication to the vaccine  
- immunocompromised subjects (in particular AIDS subjects, transplant recipients or patients receiving immunosuppressive drugs)  
- situations in which the vaccine only provides limited protection against the circulating strain | Confirmation of **insufficient** AB in children and adults without comorbidity  
Confirmation of **low** AB in the populations at risk of complication:  
children over 1 year of age with comorbidity, adults from 13 to 64 years of age with comorbidity and adults over 65 years of age.  
Confirmation of **moderate** AB in the particular case of at-risk subjects:  
- subjects living in institutions (institutionalised patients)  
- subjects with contraindication to the vaccine  
- immunocompromised subjects (in particular AIDS subjects, transplant recipients or patients receiving immunosuppressive drugs)  
- situations in which the vaccine only provides limited protection against the circulating strain |
| Exceptional situation | - | - |
## Inclusion on the list/rates and methods of reimbursement
(Official Journal dated 26 January 2010)

<table>
<thead>
<tr>
<th>Curative treatment</th>
<th>Inclusion for hospital use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>National Insurance inclusion and 30% reimbursement in at-risk subjects,(^1) adults and children over 1 year of age living or staying together and presenting typical influenza symptoms during virus circulation period.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-contact prophylaxis</th>
<th>Inclusion for hospital use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>National Insurance inclusion and 30% reimbursement - in at-risk subjects,(^1) adults and children over 1 year of age. - in the particular case of contraindication to the influenza vaccination in people suffering from asthma and COPD, children and adolescents (1 to 18 years of age) whose state of health requires prolonged treatment with acetylsalicylic acid and people staying in a healthcare organisation (HCO) mid to long term whatever their age.</td>
</tr>
</tbody>
</table>

\(^1\)At-risk subjects:
People over 65 years of age.
People suffering from the following long term illnesses: insulin-dependent diabetes, non-insulin-dependent diabetes which could not be controlled by diet alone; incapacitating stroke; severe chronic kidney disease and pure primary nephritic syndrome; severe form of a neuromuscular disease (including myopathy); cystic fibrosis; poorly tolerated congenital cardiopathy, severe heart failure and severe valve disease; severe chronic respiratory failure (including asthma on the chronic (long-term) condition list); primary severe immunodeficiency requiring prolonged treatment, infection with the human immunodeficiency virus (in people with HIV, recent studies have shown that the vaccination can cause a transient increase in the viral load and that there was no reason to recommend it routinely); homozygote sickle-cell anaemia (congenital haemolytic anaemia with haemoglobinopathy); immunocompromised patients (notably patients with transplants, patients on immunosuppressants).
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient
Oseltamivir phosphate

1.2 Indication

“Treatment of influenza:
In patients one year of age and older who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within two days of first onset of symptoms. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

TAMIFLU is indicated for the treatment of infants less than 12 months of age during a pandemic influenza outbreak.

Prevention of influenza
- Post -exposure prevention: in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.
- The appropriate use of TAMIFLU for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in the case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.
- TAMIFLU is indicated for post-exposure prevention of influenza in infants less than 12 months of age during a pandemic influenza outbreak.

TAMIFLU is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations.

Based upon limited pharmacokinetic and safety data, TAMIFLU is indicated for the treatment of infants less than 12 months of age during a pandemic influenza outbreak. The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child.”

Changes appear in bold
1.3 Dosage

"Influenza treatment"

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

- **Adolescents (13 to 17 years of age) and adults:** The recommended oral dosage is 75 mg oseltamivir twice daily for five days.

- **Infants and children 1 year of age or older:** TAMIFLU 30 mg and 45 mg capsules and oral suspension are available for infants and children 1 year of age or older. The following weight-adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Recommended dose for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 kg</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt; 15 kg to 23 kg</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt; 23 kg to 40 kg</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg twice daily</td>
</tr>
</tbody>
</table>

- **For infants less than 1 year of age:** The recommended treatment dose for infants less than 12 months of age is between 2 mg/kg twice daily and 3 mg/kg twice daily during a pandemic influenza outbreak. This is based upon limited pharmacokinetic data indicating that these doses provide plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in older children and adults. The following age-adjusted dosing regimens are recommended for treatment of infants less than 1 year of age:

<table>
<thead>
<tr>
<th>Age of infant</th>
<th>Recommended dose for 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 months to 12 months</td>
<td>3 mg/kg twice daily</td>
</tr>
<tr>
<td>&gt;1 months to 3 months</td>
<td>2.5 mg/kg twice daily</td>
</tr>
<tr>
<td>0 months to 1 month*</td>
<td>2 mg/kg twice daily</td>
</tr>
</tbody>
</table>

* There is no data available regarding the administration of TAMIFLU to infants less than one month of age.

**Influenza prevention**

**Post-exposure prevention**

- **Adolescents (13 to 17 years of age) and adults:** The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

- **Infants and children 1 year of age or older:** TAMIFLU 30 mg and 45 mg capsules and oral suspension are available.

The recommended post-exposure prevention dose of TAMIFLU is:

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Recommended dose for 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 kg</td>
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<td>60 mg once daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>
• **For infants less than 1 year of age:** The recommended prophylaxis dose for infants less than 12 months of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimens are recommended for infants less than 1 year of age:

<table>
<thead>
<tr>
<th>Age of infant</th>
<th>Recommended dose for 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 months to 12 months</td>
<td>3 mg/kg once daily</td>
</tr>
<tr>
<td>&gt;1 month to 3 months</td>
<td>2.5 mg/kg once daily</td>
</tr>
<tr>
<td>0 months to 1 month*</td>
<td>2 mg/kg once daily</td>
</tr>
</tbody>
</table>

*There is no data available regarding the administration of TAMIFLU to infants less than one month of age.

**Prevention during an influenza epidemic**
The recommended dosage for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to six weeks.

2. **DATA ON THE USE OF THE MEDICINAL PRODUCT**

According to data extracted from the IMS/Dorema database (mobile annual cumulative May 2011), TAMIFLU was prescribed 143,000 times. In 99% of cases, the reason for prescription was influenza or prophylactic measures. The average duration of prescription was 5.1 days; the average dosage was 2 tablets/day. These average treatment durations and dosages were very close to the recommended duration and dosage for curative influenza treatment; this raises a question of prescriptions predominantly for curative treatment.
3. ANALYSIS OF AVAILABLE DATA

3.1 Re-assessment of curative influenza treatment in exceptional situations and in periods of virus circulation

3.1.1 Context

After the 2009 influenza pandemic, the Ministry of Health wanted to focus on the available efficacy data on curative influenza treatment in a pandemic situation. A literature review was performed by the HAS.

In addition, the laboratory requested re-assessment of the AB and the allocation of a moderate AB for curative influenza treatment both in exceptional situations and situations of seasonal epidemics during periods of virus circulation. In these indications, the AB is currently considered as insufficient. The laboratory has provided, in support of the application, a literature review on the benefit of TAMIFLU during influenza pandemics.

3.1.2 Reminder about the previous data assessments on curative influenza treatment

The following data and conclusions evaluate the effect of TAMIFLU as a curative influenza treatment during periods of virus circulation, only in periods of ordinary seasonal epidemics.

3.1.2.1 Initial assessment in 2004

The Committee, in its opinion of 11 February 2004, concluded on the efficacy and tolerance data for TAMIFLU as a curative influenza treatment in the following terms:

"Efficacy on the symptoms of influenza:
The effect of TAMIFLU in the curative treatment of influenza has been shown on a symptomatic criterion. This effect was limited (reduction of influenza duration by around one day) and was not consistently revealed in the studies, particularly those including the populations at risk of complications (adults with comorbidity, subjects over 65 years of age or asthmatic children).

Efficacy on the complications linked to influenza:
- In the at risk complications population studied (asthmatic children, adults with comorbidity and subjects over 65 years of age), concrete proof of reduced morbidity and mortality linked to influenza are limited.
- In healthy children, a modest effect on the reduction of complications requiring antibiotic therapy was revealed. The reduction was not significant on the treated population in a practical situation but remains in favour of oseltamivir (18% vs. 22%, NS, ITT).
- In the sub-population of children of 1 to 5 years of age, treatment with oseltamivir started within 48 hours allowed a 6% reduction (23% vs. 29%) of the incidence of acute otitis media in comparison to the placebo group.
- In asthmatic children, complications reduction has not been demonstrated.
- In subjects over 65 years of age, in the pooled analyses, oseltamivir reduced the incidence of complications of the lower respiratory tract by 7% (19% vs. 12%, ITT i pop., p = 0.0156). The data evaluating the reduction in hospitalisations, based on results from undetailed pooled studies, did not allow any conclusions to be drawn.
In the population of adolescents and adults of 13 to 64 years of age, the pooled analyses revealed:
- reduction in the incidence of pneumonia (6/1547 (0.4%) versus 16/1099 (1.5%)) in favour of oseltamivir (p< 0.05, ITT)
- reduction of the number of patients with lower respiratory tract complications treated with antibiotics: 12.7% (135/1063) in the placebo group versus 8.6% (116/1350) in the oseltamivir group (p< 0.0012, ITT)

Adverse effects:
Nausea and vomiting were most commonly observed in patients receiving oseltamivir in comparison to the placebo group (around 8 to 10% of patients treated with oseltamivir). These gastrointestinal adverse effects have mostly been of mild to moderate intensity.

In addition, symptomatic efficacy of oseltamivir appeared identical in vaccinated and unvaccinated subjects.

The efficacy of TAMIFLU in influenza treatment was mainly demonstrated in patients without comorbidity. The symptomatic effect is modest and without notable public health benefit in these populations.

In subjects over 65 years of age and at-risk subjects, TAMIFLU has an expected modest impact on public health.”

3.1.2.2 Re-assessment of the 2006 AB

In 2006, to support an application for re-assessment of the AB, the laboratory provided an American, retrospective, cohort study (NORDSTROM\(^2\)). This is a comparative, retrospective, cohort study (patients treated with TAMIFLU/untreated) in patients from the Ingenix Research Database. The objective of this study was to evaluate the incidence of occurrence of pneumonia requiring a prescription of antibiotics or hospitalisation during the 30 days following the onset of influenza in 11,632 patients treated with TAMIFLU and 60,427 untreated patients.

In its opinion of 21 June 2006, the Committee concluded that: “this cohort retrospective study, performed only in the USA and in which the comparability of the groups is not established (average age different between the two groups, initial severity of influenza not determined), cannot be taken into account to evaluate the reduction in complications or hospitalisations linked to influenza.”

3.1.2.3 Assessment in 2008

In its opinion of 16 April 2008, the Transparency Committee gave its opinion on the Cosmos post-registration study into the prophylactic treatment of influenza which it requested and on the new studies submitted by the laboratory on the prophylactic and curative treatment of influenza.

“As a curative treatment, in a retrospective cohort study in Hong Kong, taking oseltamivir within the 48 hours following the onset of symptoms was associated with reduced duration of hospitalisation. This study presents methodological limitations and confirmed the data which had already been examined by the Transparency Committee”.

These data did not lead the Committee to change its conclusion: insufficient AB.

3.1.2.4 Assessment in 2009

In its opinion on the renewal of inclusion on the list of medicines reimbursed by National Insurance of 21 October 2009, the Committee examined four American retrospective studies on the at-risk populations in which TAMIFLU was used as a curative influenza treatment. Its conclusions were as follows: “As part of a curative treatment, retrospective cohort studies revealed the association of a reduction of some complications from influenza in at-risk patients treated with oseltamivir. However, these studies, with low level of evidence, performed only in the USA in selected populations, cannot be taken into account to evaluate the reduction in complications and/or hospitalisations linked to seasonal influenza in France in at-risk populations.”

3.1.3 Data on the 2009 influenza pandemic

3.1.3.1 Epidemiological characteristics

According to the data from the INVS (BEH) during the 2009-2010 epidemic:
- between 13% and 24% of the metropolitan French population were infected by the influenza A H1N1 virus (sentinel type surveillance systems).
- the number of patients was 5.1 million.
- the number of consultations was 3.5 million (sentinel network),
- the level of hospitalisation was around 1% of the consultations, i.e. 35,000 hospitalisations (measured by the sentinel network),
- the number of deaths was 312 (death certificates related to diagnosis of influenza, probably underestimated).

From studying the death certificates, the demographic characteristics of deaths linked to influenza in 2009-2010 were atypical in comparison to previous years: the population affected was much younger: mean age of death was 59.4 in 2009-2010 vs. 81.7 for the previous epidemics after the year 2000.

After standardisation on age, comorbidities of the deceased subjects were however similar to those in previous years: chronic respiratory pathology including asthma, pregnancy, acquired or iatrogenic immune deficiency, diabetes, morbid obesity and heart failure.

3.1.3.2 Use of TAMIFLU during the A (H1N1) pandemic in 2009

Before the 21 December 2009, TAMIFLU was available according to a classic distribution pattern, and until 10 December its prescription was only recommended in certain cases of influenza (severe clinical form, particular risk factors, complications from the outset).

Out of the 724 serious hospitalised cases reported to the INVS on 16 December 2009, the antiviral treatment methods were reported in 50% of cases and a third of the patients received treatment with TAMIFLU within 48 hours (132/374). This surveillance data appears to confirm the practical difficulties linked to the treatment initiation time in practice and the difficulties in identifying severe patients.

On the 21 December 2009, TAMIFLU was made freely available in retail pharmacies. Its routine prescription was therefore recommended in all cases of clinical influenza. The experience gained during this period is limited insofar as a majority of the antiviral stocks was not used in France.

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4 P. Vicente. Spécificité des caractéristiques de la mortalité liée à la grippe lors de la pandémie de grippe A (H1N1) en 2009-2010 en France. BEH Jan 2011 n°1 p1-5.
3.1.4 New efficacy data on curative influenza treatment during the pandemic period in 2009

During its literature search, HAS selected references published between January 2005 and October 2010, including articles in French, English, Spanish and Italian in the Medline, Embase and Pascal databases. The research aimed at identifying the following types of publication: recommendations, consensus conferences, meta-analyses, systematic reviews, clinical trials and cohort studies. The literature reviews were also researched as were the publications from the French teams regardless of the document type.

Secondly, only the publications with a better evidence level, presenting results on the use of TAMIFLU as a curative treatment during the pandemic influenza; were selected.

The laboratory provided a literature search from the PubMed database based on references published between 1 January 2009 and 31 July 2010. Amongst these references, the laboratory selected clinical studies which appeared the most relevant regarding the methodology criteria.

The studies found from these two searches are presented in the table in appendix 1. Only results concerning TAMIFLU and results of the main criteria, when clear, are listed in the table.

Summary of the results presented in the table (appendix 1)

No new clinical trial aimed at studying efficacy was found.

Around twenty observational studies were identified, including data on antivirals or more specifically on oseltamivir. These are presented in appendix 1.

None of these studies were performed specifically to demonstrate TAMIFLU’s efficacy. Their aim was to describe the influenza epidemic or to study the severity risk factors.

These studies appeared to reveal a link between early treatment and the severity of influenza progression. The main ones are as follows:

- The Chinese study by Yu followed 1291 influenza patients at the beginning of the influenza epidemic in China. All the influenza cases were hospitalised regardless of the level of severity, 76% of patients were treated with oseltamivir. The results regarding the treatment with oseltamivir were as follows: multivariate analysis revealed a link between lung damage and treatment with oseltamivir within the first two days following onset of symptoms: amongst the patients without lung damage, 50% were treated within the first 48 hours with oseltamivir and amongst the patients with pneumonia (110 cases), 15% were treated with oseltamivir within the first 48 hours (OR = 0.12; 95%CI = [0.08 – 0.18]).

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*Keywords used for the HAS research were [grippe (OR grippal OR grippaux) OR influenza OR influenza virus] and [oseltamivir OR Tamiflu]*

*The laboratory selection was made on the words: “H1N1” and “influenza” excluding the words “resistant” and “prevention” in the title of the article. The words “oseltamivir” or “antiviral” could appear anywhere in the text.*

*Exclusion of experimental studies, Asian studies, Eurosurveillance or CDC newsletters, studies including less than 40 patients, isolated cases, specific populations apart from studies performed on pregnant women, studies not presenting efficacy data.*

The observational study by Farias\textsuperscript{11} in Argentina was conducted among 147 infants consecutively hospitalised in 17 paediatric ICUs for severe influenza. The objective was to report the epidemiological data on severe influenza in infants. The results regarding treatment with oseltamivir showed that survivors at 28 days were more often treated (86\%) with oseltamivir in the first 24 hours than the children which died within the 28 days following hospitalisation (68\%) p=0.01.

The Canadian study\textsuperscript{12} by Zarychanski was a case-control study which was conducted on all the influenza reported cases of during the first month of the pandemic in the province of Manitoba. The objective was to determine the factors associated with the severity of the disease during the influenza pandemic. Regarding the antiviral treatment (oseltamivir or another), results from 795 influenza cases for which treatment care was known (outpatient, normal hospitalisation or hospitalisation in ICU), revealed by a multivariate analysis model that time is correlated with severity of influenza progression in comparison between patients treated in ICU and those treated as outpatient OD = 8.24 (95\%CI = [2.82; 24.1]). The percentage results were not available in the publication.

Several studies were performed in pregnant women (see appendix 1), the most relevant was Siston’s study in the USA\textsuperscript{13}. It was a retrospective follow-up of all pregnant women reported cases to the Atlanta Center of Disease Control with probable or confirmed influenza between the start of April and 21st August 2009. From the 788 influenza reported cases, 509 women were hospitalised, including 115 in ICU, and 30 women died. The treatment was: antiviral in 454 cases, oseltamivir in 329 cases, oseltamivir within the first 48 hours in 148 cases, no treatment in 45 cases, unknown in 110 cases.

The number of deaths in women treated within 48 hours was 0.5\% vs. 5\% for those who were treated during the three or four following days (RR 9.9 [1.1-87.2]) (p = 0.03).

The main bias of these studies is an indication bias, namely that the treated and untreated groups were not comparable in terms of mortality risk. In fact, the treatment was physician choice (in the studies by Farias, Zarychanski or Siston) or patient choice (untreated group refused treatment in Yu’s study). The choice could be influenced by severity of the disease and risk factors and treatment time. This bias also exists in other observational studies described in the appendix and for which there is a comparison between the groups.

The other observational studies including in the appendix 1 table and during which the link between treatment time and the severity of influenza progression was analysed, also appear to reveal that treatment with oseltamivir started within the first 48 hours after the onset of symptoms is associated with less severe influenza progression.

In conclusion, even though these studies do not demonstrate the efficacy of TAMIFLU on influenza complications and even though these studies are marred by an indication bias, they appear to reveal a link between early treatment with TAMIFLU and less severe influenza complications and constitute an argument in favour of TAMIFLU efficacy.

3.1.5 New tolerance data

No specific tolerance study was provided by the laboratory or was found in the literature search by HAS. One of the observational studies on 145 patients reported the absence of serious adverse effects. The other selected studies did not study tolerance.

\textsuperscript{12}Zarychanski MD, Correlates of severe disease in patients with pandemic influenza (H1N1) virus infection CMAJ. 2010 Feb 23; 182 (3): 257-64.
\textsuperscript{13}Siston AM, Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States, JAMA 2010 Apr 21; 303 (15): 1517-25.
According to the SPC, the only common effects are nausea and vomiting. Since the previous assessment in 2009, several SPC modifications have occurred without modification of TAMIFLU’s tolerance profile; they are:
- addition of “thrombocytopenia” adverse event in February 2011 of unknown frequency,
- comments on the neuropsychiatric effects; cases have indeed been reported but the relative contribution of TAMIFLU compared to influenza remains unknown.

### 3.1.6 Opinion from HCSP

On 4 March 2011, the Haut conseil de santé publique (High Council for Public Health) published an opinion[^14] and a report entitled “Influenza pandemic: Use and size of national antiviral strategic stocks”. The HCSP opinion was based on several observational studies mentioned in the appendix of this Transparency Committee opinion and made the following conclusions regarding the efficacy of oseltamivir as a curative treatment in the MA conditions:

“Many indirect arguments, all consistent, are in favour of the efficacy of early curative treatment (<48 hours) to prevent serious forms and reduce complications and death. This efficacy is found in pregnant women and in immunocompromised subjects. In subjects without risk factor, due to the possible onset of serious forms, early routine treatment is justified from a public health benefit point of view”.

### 3.1.7 Conclusion

The data from the initial assessment of curative influenza treatment revealed minimal efficacy (reduction of one day in the duration of the influenza) in a population without particular severity factor. In this context, the Committee wished to obtain data on the efficacy of TAMIFLU in populations of patients with particular risk factors and in terms of reduction of serious influenza complications.

During the influenza A H1N1 pandemic in 2009, no clinical trial had evaluated the efficacy of TAMIFLU as an influenza treatment and only observational studies with low levels of evidence (not randomised, indication bias) were available. However, these studies are numerous and have revealed in different countries a link between early TAMIFLU treatment (less than 48 hours after the onset of symptoms) and reduced severity of influenza in comparison to absence of treatment or late treatment (started more than 48 hours after the first influenza symptoms).

The HCSP estimated on March 4th 2011 that there are “many indirect arguments, all consistent, in favour of the efficacy of early curative treatment (<48 hours) to prevent serious forms and reduce complications and death. This efficacy is found in pregnant women and in immunocompromised subjects. In subjects without risk factor, due to the possible onset of serious forms, early routine treatment is justified from a public health benefit point of view”.

The data collected during the pandemic has not changed the known tolerance profile of TAMIFLU.

**Efficacy in children less than 1 year of age as curative and prophylactic treatment during an influenza pandemic.**

The laboratory asked the HAS to take note of a SPC modification regarding the extension of indication to children of less than 1 year of age during an influenza pandemic. In an ordinary epidemic situation, TAMIFLU remains indicated from 1 year of age.

[^14]: HCSP “Opinion relating to the strategy of use of antivirals and size of national antiviral strategic stocks as part of an influenza pandemic” and work group report “Influenza pandemic: Use and size of national antiviral strategic stocks” – 4 March 2011 [http://www.hcsp.fr](http://www.hcsp.fr)
Marketing authorisation in children less than 1 year of age was granted on October 23rd 2009 during a peak incidence of the influenza pandemic in Europe.

The EMA has deferred the obligation to submit the results from the paediatric studies performed with TAMIFLU.

A paediatric investigation plan was published by the EMA on January 28th 2011; the latter provides to perform four clinical studies for which the laboratory must present the results in July 2012. This is a specific study in children less than 1 year of age (open study for dosages and tolerance), an open pharmacokinetic study on children less than 2 years of age, a randomised double blind study on efficacy and tolerance in children of 1 to 18 years of age and a dosage study on immunocompromised children from birth to 18 years of age.

These studies are on-going and the laboratory has not provided specific data for the population less than 1 year of age in support of the application.

In terms of tolerance, it is reported in the SPC that “Available safety information on oseltamivir administered for treatment of influenza in infants less than 1 year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and post marketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged 1 year and older”.

15 http://www.ema.europa.eu
4. CONCLUSIONS FROM THE TRANSPARENCY COMMITTEE

4.1 Actual clinical benefit

As a curative treatment in adults and children over 1 year of age

Influenza is an acute and highly contagious viral disease which, in most cases, is not serious and spontaneously resolves in around one week. However, in certain subjects, influenza complications may be serious and life-threatening. During pandemics, the availability of a vaccination is not guaranteed. A higher number of influenza cases are expected and the potential severity of influenza progression is unknown.

Vaccination against influenza is the cornerstone of management of this disease. It is particularly recommended in subjects at risk of complications and health care professionals.

In reported influenza cases, there is another neuraminidase inhibitor. Despite the absence of clear evidence, there appears to be a link between taking early TAMIFLU (less than 48 hours) and a reduced severity of influenza in comparison to absence of treatment or late treatment (started more than 48 hours after the first influenza symptoms). TAMIFLU tolerance appears satisfactory.

The efficacy/adverse effects ratio is low.

In this indication TAMIFLU is a curative antiviral treatment.

TAMIFLU must be prescribed in accordance with the health authority recommendations. In 2011, the prescription of an antiviral to all suspected influenza cases was not systematic. Initiation of curative antiviral treatment is recommended

- in subjects whose clinical presentation is judged severe by the physicians or complicated from the outset
- if there are particular risk factors
- in pregnant women.

Public health benefit

- In the situation of seasonal influenza, influenza is a common contagious disease, which can be serious in certain patient’s categories (comorbidities and/or age over 65 years in particular). It constitutes a moderate public health burden.

Reducing the level of influenza morbidity and mortality during epidemics is a public health requirement. This requirement is generally covered with vaccination.

In absence of new available data on seasonal epidemics, the expected impact in terms of morbidity and mortality for this proprietary medicinal product remains unquantifiable due to the absence of data on mortality, the low effect on the morbidity criteria and the difficulties encountered in practice in initiating early treatment.

Consequently, TAMIFLU does not have a public health benefit in this indication.
In exceptional situations in the course of which the vaccination cover is not
guaranteed or is not optimal (pandemic situation and early unavailability of the
vaccinations, epidemic situation with mismatch between the vaccination viral strain
and circulating strain), neuraminidase inhibitors, including TAMIFLU, could have a
particular public health benefit.

In pandemic situations in particular, the influenza burden could be significant
depending on the epidemiology of the pandemic strain and in particular its virulence
(attack rates, at-risk populations, level of fatalities, level of hospitalisations).
The disease burden corresponding to the population treated with TAMIFLU will
however depend on authorities’ usage recommendations.

Reducing the level of influenza morbidity and mortality is generally a public health
requirement. If this requirement is not optimally covered by vaccination or other
implemented prevention measures, then antivirals are likely to provide additional
response.

However, the morbidity-mortality impact of TAMIFLU related to a pandemic strain is
unknown. The available clinical studies data does not allow quantification of the
expected impact of TAMIFLU in these circumstances due to the absence of available
data on mortality and the low effect on the morbidity criteria.

The observational study results during the A (H1N1) 2009 pandemic do not allow
evaluating this impact. However, they indicate the difficulty in accessing treatment
during the 48 hours following the onset of symptoms (potentially negative impact on
the organisation of care).

In addition, a risk of a negative public health impact on morbidity and mortality cannot
be excluded if the acceptability and use of TAMIFLU was likely to induce a reduction
in the vaccination cover and if resistance phenomena were emerging in the case of
large exposure to the product.

Consequently, in exceptional situation, a particular public health benefit is expected
for TAMIFLU but with the current state of knowledge, this benefit remains
unquantifiable.

The actual benefit of TAMIFLU as a curative influenza treatment, when initiated within 48
hours of the onset of symptoms, during a period of ordinary influenza epidemic or a
pandemic period is low in:
- subjects with clinical presentation of influenza judged severe by the physicians or
  complicated from outset,
- subjects with particular risk factors, including pregnant women.

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16The populations thought to be at risk of complications were defined for the 2010/11 epidemic by the HCSP in its
- Infants less than 2 years of age with one of the following conditions:
  - Bronchopulmonary dysplasia treated during the previous six months with mechanical ventilation and/or
    prolonged oxygen therapy and/or continuous medical treatment (corticosteroids; bronchodilators; diuretics);
  - Cyanosing or haemodynamically significant cardiopathy;
  - premature gestational age < 32 weeks;
  - cystic fibrosis;
  - malformation of the upper respiratory tracts, lower respiratory tracts, lungs or rib cage;
  - chronic interstitial pulmonary condition;
  - neuromuscular condition;
  - acquired or congenital immunity abnormalities;
- children and adolescents (up to 18 years of age) whose health requires prolonged treatment with
  acetilsalicylic acid;
- pregnant women, particularly after the 2nd trimester of pregnancy;
The actual benefit in influenza treatment is **insufficient** in other situations.

The actual benefit in prophylactic influenza treatment remains unchanged.

**In children less than 1 year of age during a pandemic**

In infants less than 1 year of age, influenza complications are particularly feared.

The efficacy of TAMIFLU as a curative influenza treatment has not been demonstrated to date, and it is extrapolated from data in infants over 1 year of age. Tolerance has been evaluated in a small number of children less than 1 year of age.

In cases of reported influenza, there is no alternative treatment. As a prophylaxis, there are alternative prophylactic treatments with the early curative treatment of contact people and barrier measures.

**TAMIFLU is an antiviral treatment for curative and prophylactic treatment.**

During the influenza pandemic, the health authorities recommended treating infants of less than 1 year of age with influenza and with a risk factor for serious influenza and infants without influenza as post-exposure treatment if there is a risk factor for serious influenza.

**Public health benefit**

In pandemic situations, the influenza burden could be significant depending on the epidemiology of the pandemic strain and in particular its virulence (attack rates, populations at-risk, level of fatalities, level of hospitalisations).

The disease burden corresponding to the limited population of children less than 1 year of age is lower, despite its severity, given the number of subjects involved.

Reducing the level of influenza morbidity and mortality is generally a public health requirement. If this requirement is not optimally covered by vaccinating the family of children less than 1 year of age, then antivirals are likely to provide additional response in comparison to other established prevention measures.

However, the impact of TAMIFLU in terms of morbidity and mortality in children less than 1 year of age is unknown, in particular regarding to the pandemic strain in absence of efficacy data in this age group and despite safety data which would indicate a safety profile similar to children over 1 year of age.

Consequently, in exceptional situations, in children less than 1 year of age, no public health benefit is expected for TAMIFLU.

The actual benefit as a curative treatment in pandemic periods is **low** in children less than 12 months of age.

- People including pregnant women suffering from the following conditions, whatever their age:
  - chronic bronchopulmonary conditions, including asthma, bronchopulmonary dysplasia and cystic fibrosis;
  - congenital poorly tolerated cardiopathies, severe heart failure and severe valve disease;
  - severe chronic nephropathies, pure and primitive nephrotic syndromes;
  - incapacitating stroke; severe forms of neurological and muscular conditions (including myopathy), severe epilepsy;
  - homozygote and double heterozygote sickle cell, sickle cell thalassemia disease;
  - endocrine and metabolic conditions which may be decompensated by an acute infection during an influenza pandemic;
  - immunosuppression including transplants, underlying neoplasia and immune cell deficiencies, infection with HIV, anatomical or functional asplenia and immunosuppressant treatments.
- People with obesity with body mass index greater than or equal to 30.
The actual clinical benefit as a prophylactic treatment in pandemic periods is **insufficient** in children less than 12 months of age.

### 4.2 Therapeutic use of TAMIFLU

#### 4.2.1 Curative treatment

Due to epidemiological arguments in favour of reduced complications linked to influenza, hospitalisations and death of vaccinated subjects in comparison to unvaccinated subjects, vaccination against influenza constitutes the reference influenza treatment strategy for the protection of at-risk groups.

In patients with influenza, the reference symptomatic treatment is not specific and is based on analgesic/antipyretic combinations. The place of influenza antivirals (oseltamivir and zanamivir) in the therapeutic strategy of symptomatic influenza treatment in an ordinary epidemic situation is limited.

In December 2010, the Committee against influenza updated its recommendations on influenza management during the period of influenza A (H1N1) virus circulation in 2009.

“The curative antiviral must be prescribed during the 48 hours following onset of the initial symptoms. The first administration of antiviral must be as early as possible, in particular after physician’s initial intervention.

**Adults and children of 1 year of age or more**

The prescription of an antiviral to all suspected influenza patients is not systematic. To date, the initiation of curative antiviral treatment is recommended in subjects presenting with:

- characteristic influenza syndrome, if the clinical presentation is judged severe by the physician;
- or particular risk factors, whatever the clinical severity noted by the physician;
- or serious clinical presentation from the outset or complicated after having ruled out a secondary bacterial infection (viral co-infection being possible, or probable, antiviral treatment associated with antibiotic treatment is justified).

The presence of respiratory difficulties (initial dyspnoea or secondary onset) justifies immediate hospital consultation.

These recommendations apply regardless of the patient’s influenza vaccination history [vaccinated with a monovalent pandemic vaccine against the influenza A(H1N1) 2009 virus or with a trivalent seasonal vaccination 2010-2011].

Pregnancy is a risk factor in itself for influenza with the A (H1N1) 2009 virus and especially after the second trimester. In the presence of pyrexia associated with respiratory signs, initiation of curative antiviral treatment with oseltamivir is recommended whatever the pregnancy trimester and presence or not of risk factors.

**Infants less than 1 year of age**

Clinical criteria in case of possible influenza in infants less than 1 year of age are:

- fever with temperature higher than or equal to 38.5°C;
- with or without respiratory symptoms signalling involvement of the upper or lower respiratory tracts or gastrointestinal disorders or convulsions.

In cases of suspected influenza in infants less than 1 year of age, initiation of curative antiviral treatment is recommended if there is a risk factor for severe influenza.

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17 [http://www.sante.gouv.fr/grippe.html](http://www.sante.gouv.fr/grippe.html) consulted on 21 September 2011

18 Infants less than 2 years of age with one of the following conditions:

- Bronchopulmonary dysplasia treated during the previous six months with mechanical ventilation and/or prolonged oxygen therapy and/or continuous medical treatment (corticosteroids; bronchodilators; diuretics);
- cyanosing or haemodynamically significant cardiopathy;
- premature gestational age < 32 weeks;
The Influenza control Committee recommends initiating curative antiviral treatment with oseltamivir even though this is an off-label prescription (outside terms of marketing authorisation) outside of the context of a level 6 pandemic with influenza A (H1N1)2009 declared by the WHO. Severe clinical presentations from the outset or complicated cases are hospitalised and treated. Infants without risk factor presenting with a clinical picture judged to be severe by the physician can be given antiviral treatment with hospital consultation.

Moreover, with any suspected case of influenza, checking for at-risk people amongst the patient's entourage is recommended during the consultation. In addition, barrier measures should be used (patient isolation, washing hands and wearing surgical masks)

4.2.2. Prophylactic treatment in infants under 12 months of age

In influenza case is suspected in the family of an infant less than 1 year of age who is not ill, initiation of post-exposure antiviral treatment (pre-emptive type) is recommended in the infant if there is a risk factor for severe influenza. Infants with risk factors justify hospital treatment in the presence of worsening in comparison to their baseline state.

4.3 Target population

During ordinary seasonal epidemics, number of people with clinical influenza and average age of people involved vary between years. The number of influenza patients with risk factors and justifying curative treatment is therefore impossible to quantify.

During a pandemic, the number of treatments is more significant than in seasonal epidemics but, in the same way, impossible to quantify.

In pandemic periods, the number of children less than 12 months of age with risk factors and susceptible to coming into contact with a case of influenza and presenting with influenza symptoms, largely depends on characteristics of the pandemic and cannot be quantified.

4.4 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and dosage in the Marketing Authorisation.

Packaging:

Appropriate for the prescription conditions.

Reimbursement rate: 30 %

- cystic fibrosis;
- malformation of the upper respiratory tracts, lower respiratory tracts, lungs or rib cage;
- chronic interstitial pulmonary condition;
- neuromuscular condition;
- acquired or congenital immunity abnormalities;
APPENDIX 1

Efficacy and tolerance of TAMIFLU as a curative influenza treatment
after the influenza pandemic in 2009

NEW PUBLISHED DATA

The studies summarised in the table below represent a selection of relevant articles found both by a literature search by HAS aiming to review the pandemic data on the benefit of antivirals and the research performed by the laboratory in support of its application for AB revision as a curative treatment.

“ID” reference: Literature search by HAS

“Lab” reference: literature search by Roche laboratory, studies presented in the application file for curative treatment AB revision.

In observational studies, only the ones containing analysis of treatment with oseltamivir were selected. Only the criteria with this analysis and those which could complement it are listed in this table.
<table>
<thead>
<tr>
<th>Study (HAS reference or submitted by the laboratory)</th>
<th>Objective</th>
<th>Methodology</th>
<th>Number of included patients</th>
<th>Treatments</th>
<th>Primary and secondary endpoint involving TAMIFLU</th>
<th>Results</th>
<th>Tolerance data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID 81 - Yu H</td>
<td>Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China BMJ (Clinical research ed.) 2010; 341 pc4779</td>
<td>Description of clinical aspects and efficacy of oseltamivir during the 2009 pandemic. Retrospective follow-up of a cohort of confirmed influenza patients in China between May and June 2009. All influenza patients were hospitalised whatever the level of severity. No randomisation</td>
<td>1291 patients Adults and children, median age 20 years Comorbidity: 5 %</td>
<td>76% of patient were treated with oseltamivir, 85% of which within the first 2 days after the onset of symptoms (no other antivirals)</td>
<td>Link between pulmonary involvement and treatment (multivariate analysis in logistic regression) Number of patients in ICU Link between pulmonary involvement and treatment with oseltamivir within the first 2 days following onset of symptoms OR = 0.12; 95%CI: 0.08 – 0.18, Link between pulmonary involvement and treatment with oseltamivir more than 2 days following onset of symptoms OR = 0.09; 95%CI: 0.05 – 0.15</td>
<td>None</td>
<td>No tolerance data in the publication.</td>
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China
| ID69 | The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. | Comparison of the viral load in infected patients with or without oseltamivir treatment. | Retrospective cohort of all confirmed influenza cases seen between April and June 2009 in the 3 hospitals in Hong Kong, hospitalised or not. Comparison between treated and untreated groups. No randomisation between groups. 145 patients included 52% less than 18 years of age, none less than 1 year of age. Non-serious patients (1 with radiological pulmonary involvement) Treatment was offered to all patients Those who refused formed the untreated group (37) Treated group (108) | Treatment was offered to all patients | Comparison of the viral load between untreated/treated Untreated vs. treated maximum of 2 days after onset of symptoms Untreated vs. treated more than 2 days after onset of symptoms Time for fever to disappear | Significant difference between the 2 groups from D5: 7.29±1.55 vs. 5.03±1.50 p = 0.04 Significant difference between the 2 groups from D4 or D5: 6.90±1.80 vs. 5.09±1.41 P = 0.029 No significant difference on D4 or 5 The disappearance of fever was quicker in treated patients (1.4 days vs. 2.8 days, p = 0.012). |
| ID 57 | Patients Hospitalized with 2009 Pandemic Influenza A (H1N1) New York City, May 2009 | Establish the characteristics of the 99 first patients hospitalised for influenza H1N1 in New York in 2009 | Retrospective observational assessment With comparison between treated and untreated patients No randomisation between treated or untreated groups 99 patients in April and May 2009 Follow-up of 99 first patients declared to the CDC hospitalised with influenza confirmed by PCR 60% < 18 years 19% < 5 years 9% > 50 years Asthma in 50% of <18 years and 46% of adults 76 patients were treated with oseltamivir, 36 of which within the first 2 days after the onset of the disease | Complications | Pre-existing risk factors Duration of hospitalisation depending on treatment time | 21% of cases presented complications 4 of which died Risk factor observed in 74% of patients, most common was asthma. Patients treated with antiviral within the first 2 days of the disease had a shorter average duration of hospitalisation than those where treatment was started later. (2 days vs. 3 days; p = 0.03) | No adverse effect reported |
| Evidence of the efficacy of the different strategies of managing influenza during the 2009 pandemic | Meta-analysis (exhaustive article search) of 22 international articles, prospective and retrospective. Classification of studies into 3 categories depending on treatment in the community/hospital/ICU. No randomisation between treated or untreated groups. | Total of 3020 patients with confirmed or probable influenza during the H1N1 epidemic in 2009. International enrolment. | Patient having received antiviral treatment were 1622 in number (53.7%), amongst them only 661 only received oseltamivir. The others could have received zanamivir, amantadine, rimantadine, or a combination of 2 antivirals. Treated patient characteristics. Impact of antiviral treatment (whatever the delay) on mortality. Impact of early antiviral treatment on mortality. | Total of 529/1498 patients, for which the time of taking an antiviral was available (35.3%), received oseltamivir within the first 2 days. Out of all the patients included in the studies, 35.4% have been hospitalised in ICU and 12.8% died. No significant difference on taking oseltamivir between the patients who died and those who survived. 26% of patients over 18 years of age died vs. 54% surviving were treated within the first 2 days (p<0.001). Only 1 study studied the difference in terms of mortality depending on the precocity of treatment. (ID108- Louie JK, 2009). | No tolerance data in the publication. |
| Study on clinical and viral (viral shedding) efficacy of oseltamivir in patients with confirmed influenza H1N1 in June 2009. All confirmed cases of influenza at TTSH hospital in Singapore were hospitalised and treated. | Prospective observational study | 70 patients with confirmed influenza of which 20 (29%) with comorbidity. They were only discharged from hospital when the PCR on the nasal and pharyngeal secretions was negative. | All patients were treated with oseltamivir/5 days | The clinical effect of oseltamivir depending on the precocity of treatment. Virological effect (PCR) of oseltamivir depending on the precocity of treatment. | No difference in the respiratory symptoms between patients treated early or not (more than 48 hours after the start of treatment). In all the patients, the nasal and pharyngeal secretions remained positive 4 d +/- 2 after admission (i.e. 6d +/- 2 after onset of symptoms). A significant difference of viral shedding was found from the 7th day between patients treated early and those treated later. | No tolerance data in the publication. |
| ID90 - Farias JA – *Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina* Intensive care medicine 2010; 36 (6): p1015-1022. | To determine the clinical and epidemiological characteristics of influenza H1N1 in 2009 in a paediatric population in Argentina. | Prospective follow-up in a cohort of patients hospitalised consecutively for 1 and a half months in the 17 participating ICUs for confirmed influenza. | 147 Argentinian infants and children. | Curative oseltamivir as doctor's choice | Main criteria: mortality on D28. Secondary criteria: Comparison of treatments in survivors vs. deceased. - oseltamivir, - oseltamivir during the first 24 hours. | The level of mortality was 39% survivors at 28 days (91%) were as much treated with oseltamivir than children who died during the 28 days following hospitalisation (92%). Survivors at 28 days were more often treated (86%) with oseltamivir in the first 24 hours than the children who died during the 28 days following hospitalisation (68%), p = 0.01. | No tolerance data in the publication. |

<p>| ID 62 - Goldstein E, <em>Oseltamivir for treatment and prevention of pandemic influenza A/H1N1 virus infection in households</em> BMC infectious diseases 2010; 10 p211 | To determine the efficacy of a curative treatment with oseltamivir on the transmission of influenza within a household during the H1N1 2009 pandemic. | Prospective cohort study. No control group. Index cases of confirmed H1N1 influenza, telephone detection of secondary cases for 7 days from April to June 2009. 135 households included. | 135 households included with 1 case of confirmed influenza. | Curative treatment with oseltamivir 5 days for index cases. | Secondary attack rate in the household (= effect of curative oseltamivir on the proportion of households with one or more secondary cases). Individual secondary attack rate (= effect of oseltamivir on the proportion of infected individuals in the households). | Treatment started with oseltamivir on the same day as the onset of symptoms associated with a non-significant 42% reduction (OR 0.58, 95%CI 0.19-1.73) of the risk of secondary influenza in the household. Non-significant reduction of 50% of individual risk of influenza (OR 0.4, 95%CI 0.17-1.46). Limits reported in the publication: to be monitored with new trials. Number of households included was insufficient. | No tolerance data in the publication. |</p>
<table>
<thead>
<tr>
<th>ID108+ lab</th>
<th>Louie JK, 2009</th>
</tr>
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<tbody>
<tr>
<td>Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California</td>
<td>To determine the clinical or epidemiological risk factors of hospitalisation or death.</td>
</tr>
<tr>
<td>JAMA November 4, 2009—Vol 302, No. 17 p1886 -01</td>
<td>Retrospective follow-up of the cohort of the first 1088 patients hospitalised in California for at least 24 hours or death from probable A H1N1 influenza (influenza PCR could not be typed) or confirmed (A H1N1 PCR) from 14 June 2009.</td>
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<td>1088 patients of which 344 were children less than 18 years of age. The rate of hospitalisation or death (in relation to the general population) was globally 2.8/100,000, ranging from 11.9/100,000 in children less than 1 year of age and 1.5/100,000 after 70 years of age.</td>
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<tr>
<td></td>
<td>Amongst the characteristics recorded for the hospitalised or deceased patients, 79% of patients for which information was available (884 cases) received an antiviral (not specified), 51% received the treatment in the first 48 hours after the onset of symptoms.</td>
</tr>
<tr>
<td></td>
<td>Number of deaths: 118 deaths (8 children/110 adults).</td>
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<tr>
<td></td>
<td>Number of hospitalisations: 970 hospitalised (336 children/634 adults).</td>
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<tr>
<td></td>
<td>Comorbidity could correspond to a risk factor.</td>
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<td></td>
<td>Link between severity/death and time to taking treatment (antiviral not specified).</td>
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<tr>
<td></td>
<td>No tolerance data in the publication.</td>
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</tbody>
</table>
To determine the factors correlated to the severity of the disease during the influenza pandemic in 2009, a retrospective case/control cohort study of all the patients from the Manitoba province in Canada who had a confirmed influenza H1N1 between April and September 2009 and for whom the final location of treatment was known. Control groups were patients hospitalised for influenza outside ICU and patients monitored for influenza as an outpatient. 795 patients included.

Antiviral prescription was recommended in severe cases by the Canadian authorities. Frequency of antiviral treatment depending on the management method.

Severity of the treated cases:
- Median time between symptoms and the treatment depending on the severity
- Multivariate analysis of risk factors, results involving the antiviral

Severity of the treated cases:
- ICU/outpatient OR 8.24 (95%CI 2.82–24.1) NS
- ICU/hospitalisation outside of ICU: OR 2.4 (95%CI 0.8–7.5) NS

The time of taking the antiviral +/- 48 h is correlated to the severity of disease:
- Time <48 h associated with increased severity
- ICU/outpatient OR 8.24
- ICU/hospitalisation outside of ICU: OR 2.4 (95%CI 0.8–7.5) NS

No tolerance data in the publication.
<p>| Lab | Observational analysis of hospitalised influenza cases. Search for a link between early treatment with oseltamivir and severity of the disease. | Prospectively follow-up of the cohort of hospitalised patients for H1N1. Between 1st July and 2nd November 2009 all the cases hospitalised then until 16th December all severe cases. Influenza confirmed or probable. Comparison of severe and non-severe cases. | 513 non-severe cases 724 severe cases | Comparison of time of taking the antiviral according to severity of the cases. According to severity: - number of cases - OR calculated in comparison to non-severe cases. | Non-severe &lt;48 h: 152 &gt; 48 h or no treatment: 113 Severe or deceased &lt;48 h: 116 &gt;48 h or no treatment: 180 OR 2.1 (95% CI 1.5 - 2.9) Deceased: &lt;48 h: 16 &gt;48 h or no treatment: 62 OR 5.2 (95% CI 2.9 - 7.5) | The publication concluded on the association between severity and absence of early treatment with oseltamivir. |
| Lab | Description of clinical characteristics of a cohort of patients hospitalised for at least 24h for confirmed H1N1 between May and mid-June 2009 in the USA. Analysis of the first 272 complete medical records sent to the CDC. | Follow-up of a cohort of patients hospitalised for at least 24h for confirmed H1N1 between May and mid-June 2009 in the USA. Analysis of the first 272 complete medical records sent to the CDC. | 272 patients Median age 21 years Severity: 25% ICU 7% deceased 40% had pulmonary involvement on the radiograph. Treatment chosen by doctor. 75% of patients received an antiviral 79% received an antibiotic. | Comparison of the time of initiating treatment between severe and non-severe patients. | Percentage of patients having received an antiviral in the 48 h following the onset of symptoms: ICU or deceased: 23% Simple hospitalisation: 45% | No tolerance data in the publication. |</p>
<table>
<thead>
<tr>
<th>Labo</th>
<th>Chien YS</th>
<th>Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan</th>
<th>Retrospective follow-up of a cohort of patients declared to Taiwan CDC between 8th and 15th September 2009 and hospitalised with confirmed H1N1 influenza complicated with pulmonary involvement</th>
<th>96 patients analysed with pulmonary involvement 23% with respiratory failure of which 45% died. The patients with respiratory failure were considered as severe</th>
<th>All the patients received oseltamivir and other treatments could be antibiotics, corticosteroids.</th>
<th>Comparison of the group with respiratory failure and the group without respiratory failure looking for a severity factor (linked to respiratory failure)</th>
<th>Link between respiratory failure/time between start of symptoms and start of treatment (OR 19.3 95%CI 2.5 – 151) p&lt;0.001 Other prediction factors for severity found by multivariate analysis: level of lymphocytes ≤800/µL. SOFA score ≥4 (sepsis related organ failure assessment) The treatment time was not analysed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab</td>
<td>Lee EH – 2010</td>
<td>Fatalities associated with the 2006 H1N1 Influenza A virus in New York city</td>
<td>Clinical and demographic description of deceased patients from influenza A H1N1 in New York City from 24 April to 8 July 2009</td>
<td>Comparison to groups of reference patients (general population for the demographic/deaths for other reasons/hospitalised survivors) No randomisation, comparison to a reference population.</td>
<td>47 patients hospitalised and died from confirmed H1N1 2 (4.3%) &lt;6 months 28 (60%) between 18 and 49 years 68% were treated with oseltamivir</td>
<td>Comparison between deceased patients and surviving patients</td>
<td>More diabetes (43% vs. 11%), cardiovascular disease (25% vs. 4%) and immunosuppression (29% vs. 3%) in deceased patients. The deceased patients came to hospital later. (3 days vs. 2 days p&lt;0.05), the deceased hospitalised patients were treated later after the start of symptoms than the survivors (6.5 vs. 3 p&lt;0.01)</td>
</tr>
<tr>
<td>Lab</td>
<td>Study Title</td>
<td>Study Design</td>
<td>Study Duration</td>
<td>Study Population</td>
<td>Main Criteria</td>
<td>Secondary Criteria</td>
<td>Number of Patients Treated</td>
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<tr>
<td>Lab Torres JP 2010</td>
<td>Impact of the Novel Influenza A (H1N1) during the 2009 Autumn-Winter Season in a Large Hospital Setting in Santiago, Chile</td>
<td>Retrospective cohort of all patients received in one of the hospitals in Santiago, externally or internally, for H1N1, confirmed or not confirmed, throughout the epidemic (17th May to 17th June 2009)</td>
<td>10,048 patients with clinical diagnosis of influenza. Of which 4591 cases confirmed. Median age 13 years</td>
<td>99.4% of patients received oseltamivir, 0.3% zanamivir</td>
<td>No comparison</td>
<td>No severity criteria researched</td>
<td>99 patients hospitalised</td>
</tr>
<tr>
<td>Lab Dominguez-Cherit G - 2009</td>
<td>Critically Ill Patients With 2009 Influenza A (H1N1) in Mexico</td>
<td>Retrospective cohort of all severe hospitalised cases of confirmed, probable or suspected H1N1 Between 24th March and 1st June in 6 hospitals in Mexico</td>
<td>899 patients hospitalised for confirmed, probable or suspected influenza</td>
<td>No comparison</td>
<td>Main criteria: mortality</td>
<td>Secondary criteria: level of patients in a critical condition</td>
<td>No deaths</td>
</tr>
<tr>
<td>AT-RISK POPULATIONS</td>
<td>PROSPECTIVE COHORT STUDY IN USA AND CANADA AND HAVING A H1N1 INFLUENZA BETWEEN APRIL AND DECEMBER 2009, VIROLOGICALLY CONFIRMED. IN THE PARTICIPATING CENTRES, ALL CASES SHOULD BE INCLUDED. 242 PATIENTS</td>
<td>ADULTS ON IMMUNOSUPPRESSANTS FOLLOWING AN ORGAN TRANSPLANT 242 PATIENTS INCLUDED</td>
<td>ANTIVIRAL TREATMENT ACCORDING TO DOCTOR'S CHOICE</td>
<td>RADIOGRAPHIC SIGNS OF PULMONARY DISEASE</td>
<td>NUMBER OF PATIENTS RECEIVING ANTIVIRAL TREATMENT</td>
<td>TREATMENT TIME</td>
<td>LINK BETWEEN TREATMENT TIME AND HOSPITALISATION IN ICU</td>
</tr>
<tr>
<td>ID 64 — KUMAR D.</td>
<td>OUTCOMES FROM PANDEMIC INFLUENZA A H1N1 INFECTION IN RECIPIENTS OF SOLID-ORGAN TRANSPLANTS: A MULTICENTRE COHORT STUDY. LANCET INFECTIOUS DISEASES 2010; 10 (8): P 521-526</td>
<td>32% HAD RADIOGRAPHIC SIGNS OF PULMONARY DISEASE</td>
<td>223 PATIENTS (94%) RECEIVED CURATIVE TREATMENT WITH OSELTAMIVIR (221) OR ZANAMIVIR (1) OR BOTH (6). THOSE WHO DID NOT RECEIVE ANTIVIRAL TREATMENT WERE EITHER CURED OR HAD A VERY MILD INFLUENZA. THE TREATMENT WAS ONLY STARTED WITHIN THE FIRST 2 DAYS OF DISEASE IN 42% OF CASES. EARLY TREATMENT (WITHIN 48HOURS) WITH AN ANTIVIRAL WAS ASSOCIATED WITH A LOWER PROBABILITY OF ADMISSION INTO THE ICU. HOSPITALISATION IN ICU IN 8% OF PATIENTS TREATED WITHIN THE FIRST 2 DAYS AFTER THE ONSET OF SYMPTOMS VS. 22% OF PATIENTS TREATED AFTER THE FIRST 2 DAYS FOLLOWING THE ONSET OF SYMPTOMS. P = 0.007</td>
<td>NONE</td>
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</tbody>
</table>
**Lab**

Siston AM  
Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States  
*JAMA.* 2010 Apr 21; 303 (15):1517-25.

<table>
<thead>
<tr>
<th>Description of the severity of H1N1 influenza and the association with antiviral treatment during pregnancy in the USA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort of all pregnant women declared to the CDC for probable or confirmed influenza between the start of April and 21st August 2009.</td>
</tr>
</tbody>
</table>
| 788 declared cases  
Median age 25 years  
49% with risk factor (asthma, obesity pre-gestational, diabetes etc.) |
| Level of severity  
Hospitalisation  
ICU  
Maternal death  
Antiviral treatment of hospitalised patients  
Antiviral treatment of deceased patients  
Number of deaths according to treatment time  
Number of deaths in women treated ≤ 2 days versus 3-4 days |
| 509 hospitalised  
115 hospitalised in ICU  
30 deceased  
454 / antiviral  
329 / oseltamivir  
148 treated /time ≤ 2 days  
45 untreated  
110 treatment unknown  
25 treated with antivirals  
21 oseltamivir  
1 treated time ≤ 2 days  
5 untreated  
0 treatment unknown  
<2 days: 1 deceased  
3-4 days: 4 deceased  
>4 days: 20 deceased  
Untreated: 5 deceased  
0.5% of women treated ≤ 2 days died vs. 5.0% of women treated in 3-4 days  
RR 9.9 (1.1-87.2) p = 0.03 |
| No tolerance data in the publication. |

**Lab**

Louie JK  
Severe 2009 H1N1 influenza in pregnant and women in California.  

<table>
<thead>
<tr>
<th>To determine the severity of influenza in pregnant women during the H1N1 influenza epidemic</th>
</tr>
</thead>
</table>
| Prospective follow-up of confirmed influenza cases reported to the CDPH from 23rd April to 11th August 2009 in pregnant women, post-partum women or women of child-bearing age, hospitalised or deceased.  
Comparison of pregnant women vs. control group of non-pregnant women |
| 94 pregnant women (mostly 2nd or 3rd trimester)  
8 post-partum  
137 not pregnant at child-bearing age |
| Antiviral treatment  
Treatment time ≤2 days  
ICU hospitalisation  
Deaths |
| 81% in the 2 groups  
50% pregnant women  
34% not pregnant (NS)  
19% pregnant women  
30% not pregnant (NS)  
6/94 pregnant women  
17/137 not pregnant |
| Probable under-reporting higher for non-pregnant women,  
No tolerance data in the publication. |
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<tr>
<th>Lab</th>
<th>Creanga AA 2010</th>
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</thead>
</table>

To determine the severity and the effect of antiviral treatment on the severity of influenza during pregnancy:

- Retrospective follow-up of all women from 14 to 41 years of age, pregnant or not pregnant, hospitalised for confirmed H1N1 influenza between 24th April and 10th May 2009.

Hospitalised influenza patients:
- 62 pregnant women (55.3/100,000)
- 74 not pregnant women (7.7/100,000)

Comparison between the 2 groups:

- Frequency of severe cases (= death or hospitalisation in ICU)
  - 7/100,000 pregnant women
  - 1.7/100,000 not pregnant
- Presence of risk factors
  - 29% pregnant women
  - 67.6% not pregnant women (p = 0.001)
- Number of cases treated early with an antiviral
  - Similar in the 2 groups: 48% treated within first 2 days
- Level of severe outcome for the child (death or transfer to paediatric ICU)
  - 22 deliveries during hospitalisation for influenza: severe outcome 83.3%
  - Non-severe outcome 12.5% (p = 0.004)
- Treatment time of the severe influenza + delivery
  - 6 deliveries during hospitalisation for severe influenza. None received oseltamivir in the 48 hours

No tolerance data in the publication.
| ID73 – Infectious Diseases Society of America 2010 | - Ng S -  
| Effects of oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of influenza virus  
Hong Kong |
| Evaluation of the indirect efficacy of oseltamivir treatment of a case of influenza. |
| Prospective cohort study. Efficacy of TAMIFLU on the contagiousness in a household when curative treatment is given. The index case and their families were followed for 7 to 10 days. Clinical and virological follow-up of the contact cases. | 
Winter 2007-2008 |
| 450 index cases followed as well as their families. Of which 384 index cases of virologically confirmed influenza/amongst which 90 treated with oseltamivir. |
| Treatment of the index case at the doctor’s request in particular with oseltamivir |
| Acceleration of the recovery of the index case |
| Duration of viral carrying in the index case |
| Intra-family transmission to at least one person (analysed in 53 households) level of secondary attack (secondary attack ratio) |
| For treatment with oseltamivir in the first 48 hours (all symptoms); “acceleration factor” = 0.56 (95% CI: 0.42-0.76) i.e. halving the recovery time. No significant effect of oseltamivir on the duration of viral shedding Median duration of viral shedding 6 days. Varies with the treatment time of the index case with an antiviral since the onset of symptoms:  
untreated index case: OR 8.7% (95%CI 6.8-11)  
treated index case in the first 24 hours: OR 4.7% (95%CI 1-13)  
index case treated between 24 hours and 48 hours: OR 6.0% (95%CI 2.5-12)  
index case treated after 48 hours: OR 7.0% (95%CI 1.5-19) |
| No tolerance data in the publication. |