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Use of oseltamivir in Dutch nursing homes during the 2004–2005 influenza season

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Abstract

To assess the implementation of guidelines for using neuraminidase inhibitors in the control of influenza outbreaks in Dutch nursing homes, data were collected on prophylactic and therapeutic use of anti-viral medication, indications for use and criteria for prescribing, based on experiences during the influenza season 2004–2005 in a retrospective cross-sectional survey among Dutch nursing homes after the 2004–2005 season.

Ninety/194 (49%) participating nursing homes reported an outbreak of influenza-like illness; in 57/194 (29%) influenza was laboratory confirmed. In 37/57 homes (65%) oseltamivir had been used as prophylaxis. Prophylactic use was extended to all residents and staff in 6/37 (16%) of homes, but limited in the others. In 9/37 (24%) no staff were issued prophylaxis. Among clinicians with laboratory confirmed influenza, 41/46 (89%) had used oseltamivir therapeutically. Main reasons for not prescribing oseltamivir for prophylaxis and/or therapy were lack of scientific evidence, high costs, and absent or delayed laboratory confirmation.

Logistical bottlenecks in diagnosis, cost-effectiveness concerns, and lack of an evidence-base hamper full integration in policy and should be addressed.

Keywords: Influenza; Nursing homes; Oseltamivir

1. Introduction

Every year, human influenza virus infections lead to considerable morbidity and mortality among frail and elderly populations [1]. Seasonal variation depends on the virulence of the circulating virus strains and the amount of pre-existing (partial) immunity. Pre-season vaccination is currently the main preventive intervention, both for individual protection and to curb spreading of an outbreak. However, vaccination has only limited effectiveness among the elderly population related to the continuous antigenic drift of the virus in general and a decreased immune response to the vaccine with increasing age and with the occurrence of specific immune-suppressive co-morbidity [2]. Furthermore, immunity wanes over time during in the influenza season.

If despite vaccination an influenza outbreak occurs, antiviral treatment could offer an opportunity to reduce the duration and severity of disease, as well as to limit further spread of an outbreak [3]. The first generation antivirals (amantadine and rimantadine) were active against influenza A only. Widespread use has been further limited due to frequent central nervous system adverse effects and rapid development of resistance. With the development of neuraminidase inhibitors, a new class of antivirals has become available which has fuelled interest in their therapeutic use and also as secondary prevention through post-exposure prophylaxis

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Table 1
Baseline characteristics of participating nursing homes, by reported influenza outbreak in the 2004–2005 season (median, inter quartile range)

Category	Clinical outbreak	No outbreak	*p*
n	95	99	
Total number of residents	184 (130–280)	175 (120–240)	0.5
Total number of staff	305 (200–460)	262 (180–400)	0.4
Vaccination coverage residents (%)	90 (90–95)	90 (88–95)	0.4
Vaccination coverage staff (%)	10 (5–15)	10 (5–20)	0.9
Number of units of care	7 (5–11)	7 (5–11)	1.0
Number of clinicians	4 (3–7)	4 (3–5)	0.8
Years of experience as clinician	16 (12–23)	16 (13–21)	0.9

(PEP). So far, few contra-indications and side effects have been reported, and hardly any drug resistance. Oseltamivir looks particularly promising as it can be taken orally, is licensed for therapeutic and prophylactic use (both in contrast to zanamivir, the other neuraminidase inhibitor available) and is active against influenza A and B (in contrast to the first generation antivirals) [4].

In 2004, the Dutch association of nursing home physicians (NVVA) and the national coordinating structure infectious disease control (LCI) issued guidelines in which they cautiously supported the use of oseltamivir both therapeutically and prophylactic for affected units of care in case of an influenza outbreak in a nursing home [5,6]. These guidelines led to much discussion in the Dutch medical community. This paper reports on the evaluation of the implementation of the guidelines in Dutch nursing homes during the 2004–2005 influenza season, and their role in the control of influenza outbreaks.

2. Materials and methods

In 2004–2005, the influenza season in the Netherlands occured between week 44, 2004 and week 12, 2005. After a pilot phase, all 348 Dutch nursing homes were sent a questionnaire in April 2005, at the end of the season.

Data were collected on characteristics of the nursing home (size, vaccination coverage) and occurrence of one or more (clinical) influenza outbreaks in the 2005–2005 season. If an outbreak had occurred, further details were asked, including the use of antiviral medication. If no or only partial antiviral medication was used during an outbreak, reasons for not using them were assessed, both for therapeutic and prophylactic use. Furthermore, clinicians were asked to score criteria for prescription on a scale between 1 ('of no importance') and 5 ('of great importance').

A telephonic follow-up was conducted among a 25% sample of final non-responders.

2.1. Definitions

A confirmed outbreak was defined as the occurrence of more than one influenza-like illness case in a unit of care, of which at least one was laboratory confirmed.

A unit of care was defined as a set group of residents who are under the care of a fixed group of staff (both permanent and temporary).

Data were entered in Microsoft Access 2002, and analysed using Stata 8.0 (Stata Corp, TX, USA). Proportions were compared using chi-square testing, differences between medians were assessed using Wilcoxon testing.

Ethical approval was not indicated as this study involved retrospective data collection at institution level only.

3. Results

3.1. Nursing homes

Information for 194/348 (56%) of nursing homes was received by questionnaire. In 95/194 (49%) homes, a clinical outbreak was observed in the 2004–2005 season. Table 1 summarizes baseline characteristics of the participating homes. There was no difference in vaccination coverage of residents or staff between houses with and without an outbreak.

3.2. Influenza outbreaks

The median number of units involved was 2 (range 1–12). The median number of affected residents was 14 (range 1–84), and of affected staff 12 (range 2–68).

In 64/95 (67%) nursing homes with a reported clinical outbreak, laboratory tests were requested for virological confirmation. In none of the nursing homes a near-patient test was used to seek virological confirmation. The majority (54/64, 84%) had requested a 'fast track' laboratory test (which could be a variety of tests including PCR) from a nearby laboratory, sometimes combined with other more time-consuming diagnostics, such as culture. In 7/64 (11%) homes, the diagnosis of influenza was not virologically confirmed. Thus, overall 57/194 (29%) of Dutch nursing homes had a laboratory confirmed influenza outbreak during the 2004–2005 season.

3.3. Anti-viral prophylaxis

In 37/57 (65%) nursing homes with a laboratory confirmed outbreak, antiviral PEP was prescribed, as well as in one

Table 2
Reasons for not prescribing antiviral post-exposition prophylaxis during an influenza outbreak (*n*, %)

	Total	Confirmed outbreak	No (confirmed) outbreak	*p*
Nursing homes[a]	136	57	79	
No influenza on unit	86 (63)	27 (47)	59 (75)	0.001
Lack of evidence-base	46 (34)	16 (28)	30 (38)	0.2
Influenza mild	43 (32)	14 (25)	29 (37)	0.1
Costs	42 (31)	16 (28)	26 (33)	0.7
No or late laboratory confirmation	41 (30)	11 (19)	30 (38)	0.02
No operational outbreakplan	36 (26)	9 (16)	27 (34)	0.02
Other prevention	30 (22)	26 (46)	4 (5)	<0.001
Should be implemented by GP[b]	24 (18)	10 (18)	14 (18)	1.0
Vaccination should be sufficient	22 (16)	5 (9)	17 (22)	0.05
Side-effects	17 (13)	11 (19)	6 (8)	0.04
Ethical objections	16 (12)	5 (9)	11 (14)	0.4
Lack of support among staff[b]	16 (12)	10 (18)	6 (8)	0.08
Logistical impediments	16 (12)	8 (14)	8 (10)	0.5
Other reasons	21 (16)	17 (30)	4 (5)	<0.001

[a] More than one reason per nursing home possible.
[b] Relates to prophylaxis of staff only.

nursing home in the absence of virological confirmation. The median duration of PEP was 8 days for residents (range 2–14) and 9 days for staff (range 7–14). Start of PEP for residents occurred after a median of 48 h (range 4–336), and for staff after a median of 66 h (range 16–336) following the start of the outbreak. All but one of the homes used oseltamivir, the exception used amantadine (Table 2).

In 9/37 (24%) homes, PEP prescription was not extended to staff and limited to residents only. PEP was usually limited to the affected units (28/37, 76%), although in 6 homes (16%) it was offered to all residents and staff of the nursing home. In the remaining homes PEP was offered to some but not all in affected units, related to logistical and medical reasons. The median number of residents receiving PEP was 50 (range 4–150), and of staff 40 (range 10–292). Reasons for not prescribing PEP to all or some residents and staff are summarised in Table 3, as reported by homes with and without a confirmed outbreak. Clinical judgement on the severity of the outbreak was a strong factor, while lack of evidence on efficacy in nursing homes, high costs, and uncertainty of the diagnosis in the absence of rapid laboratory confirmation, were important reasons not to prescribe antiviral PEP. The importance given to the presence of an operational outbreak plan to address the occurrence of an outbreak supports the need for early planning and preparation. Both gastro-intestinal side-effects and allergic skin reactions were mentioned as potential adverse effects.

It should be noted that 56/57 (98%) of nursing homes with, and 39/137 (29%) of nursing homes without a confirmed outbreak implemented other preventive measures to reduce the impact of an outbreak. These preventive measures included increasing awareness among staff (62%), introduction of cohort nursing (57%), physical separation of residents (38%) and cancellation of group activities (53%), wearing of facial masks (53%), and intensified manual hygiene (66%).

3.4. Antiviral therapy

Seventy-four/200 (37%) participating clinicians had diagnosed influenza on their units of care, and 52/74 (70%) had asked for laboratory confirmation. Forty-six/52 (88%) clinicians had their clinical diagnosis of influenza virologically confirmed. Most of these clinicians (41/46, 89%) with confirmed influenza had prescribed antiviral therapy, as well as six clinicians who did not have laboratory confirmation of the outbreak. All clinicians prescribed oseltamivir. Median duration of therapeutic use was 5 days (range 2–11), which was started after a median of 24 h following the clinical diagnosis.

Half (23/46, 50%) of the clinicians with a confirmed outbreak on one of their units, prescribed antiviral therapy to

Table 3
Reasons for not prescribing antiviral therapy during an influenza outbreak (*n*, %)

	Total	Confirmed outbreak	No (confirmed) outbreak	*p*
Nursing homes[a]	49	23	26	
Clinical judgement	27 (55)	16 (70)	11 (42)	0.06
No operational outbreakplan	17 (35)	2 (9)	15 (58)	<0.001
No or late laboratory confirmation	15 (31)	1 (4)	14 (54)	<0.001
Ethical objections	10 (20)	6 (26)	4 (15)	0.4
Costs	3 (6)	2 (9)	1 (4)	0.5
Side-effects	2 (4)	2 (9)	0	0.1
Other reasons	6 (12)	5 (22)	1 (4)	0.06

[a] More than one reason per nursing home possible.

Table 4
Importance allocated to specified criteria which influence the decision in Dutch nursing homes to use antivirals as prophylaxis or therapy, ordered by median weight (scale 1–5)

	Prophylaxis	Therapy
Important or very important (score ≥4)		
Presence of more than one clinical influenza patient, with at least one virological confirmation within the *unit of care* within 48 h.	5	5
Number of laboratory confirmed influenza patients within the *nursing home*	5	4
Number of laboratory confirmed influenza patients within the *unit of care*	5	4
Number of clinical influenza patients (residents and staff) within the *unit of care*	5	3
Presence of an influenza outbreak plan in the nursing home	4	4
Presence of more than one clinical influenza patient, with at least one virological confirmation within the *nursing home* within 48 h	4	4
Laboratory confirmation of the patient	–	5
Severity of clinical influenza of the patient	–	4
Opinion of the patient and/or family	–	4
Some importance (score > 2 but score < 4)		
Number of clinical influenza patients (residents and staff) within the *nursing home*	4	3
Number of staff on sick leave within the *unit of care,* possible related to influenza	4	3
Experiences during previous influenza outbreaks	4	3
Accuracy of match between the vaccine and circulating virus	4	3
Awareness of the severity of the epidemic in the outside community	4	3
Baseline clinical profile (including age) of patients on the unit of care	3	4
Number of staff on sick leave within the *nursing home*, possible related to influenza	3	3
Known influenza outbreaks in other nursing homes in the same season	3	3
Residents use common spaces	3	–
Ongoing communal activities of residents	3	–
Other preventive measures in nursing home or unit	3	–
Absence of cohort nursing	3	–
Increased mortality on unit of care	–	3
Vaccination coverage among residents on unit of care	3	2
Vaccination coverage among staff on unit of care	3	2
Costs for nursing home	3	1
Little of no importance (score ≤ 2)		
Type of unit of care	2	2
Absence of facial masks being worn by staff	2	–
Vaccination status of patient	–	2
Total number of residents of the nursing home	1	–
Total number of residents on the unit of care	1	–
Total number of staff of nursing home	1	–
Total number of staff on the unit of care	1	–

all their patients on an affected unit, 5 (11%) to none of their patients, and the others (18, 39%) to some patients. The main reasons for not prescribing antiviral mediation to (some) patients are summarised in Table 4. Included are answers from five clinicians who prescribed some oseltamivir despite a negative laboratory diagnosis, as well as from 21 clinicians who suspected influenza but did not ask for laboratory confirmation. Clinicians whose clinical diagnosis was not supported by a virological diagnosis indicated that the lack of laboratory confirmation and the lack of an operational outbreak plan were major factors for not prescribing antiviral therapy, while for those with laboratory confirmation, ethical reasons were a major factor.

3.5. Criteria for prescribing of antivirals

Table 4 gives an overview of the weight given to a set of specified criteria which could impact on the decision to implement the use of antivirals. Most, but not all, criteria could be scored for both PEP and therapeutic use. For prophylactic use, most weight was given to clinical and laboratory confirmation of influenza on the unit of care. For therapeutic use, laboratory confirmation of the patient was given most weight. Apart from the weight given to costs, there was little difference between the weight of criteria in using antivirals for PEP or for therapy.

3.6. Qualitative feedback

Several nursing homes gave additional comments on the use of antivirals, which could be divided into categories:

(a) Official guidelines: ‘lack of consultation before implementation’, perceived ‘inconsistencies’, ‘vagueness’ or ‘gaps’ in the guideline, ‘difficult to implement’.
(b) Outbreak plan: ‘in preparation’, ‘modified’ from official guidelines.

(c) Ethical objections: 'medicalisation', 'moral pressure on staff'.
(d) Priorities in care: 'biscuits versus oseltamivir', 'increased workload versus limited reduction in disease duration'.

3.7. Non-responders

Forty/153 (25%) non-responders were contacted by telephone as follow-up. The main reason for non-response given was lack of time (16/40). From six nursing homes, a completed questionnaire was still received and included. Of the non-responders, 8/30 (27%) indicated to have experienced influenza during the 2004–2005 influenza season in their nursing home, which was confirmed for four of them. Three/four nursing homes had used oseltamivir as therapy, and one also as PEP. Reasons mentioned for not prescribing oseltamivir were lack of evidence base (3×), costs, lack of an operational outbreak plan, side-effects, and (among staff) lack of support (all 1×).

4. Discussion

The principal finding of our study was that in spite of significant reservations being raised by over a third of participating nursing homes about the guidelines on antiviral use in nursing homes, nearly 90% of affected units of care implemented at least some therapeutic use of antivirals and nearly two-thirds of affected homes prescribed at least some PEP with antivirals.

The main concern was the current lack of evidence for the recommendation to prescribe oseltamivir in nursing homes. Studies so far have suggested, but not proven that anti-virals could be effective in nursing homes in reducing transmission when used as PEP [7]. Experimental research [8], observational studies in healthy adults [9] and trials among health family members [10,11] did show an effect of oseltamivir in interrupting transmission. A recent observational study in eight nursing homes showed a reduced incidence of influenza among residents who received PEP with oseltamivir [12]. This was not a randomised study however, and reduction of the influenza activity can have coincided with a reduction of the epidemic activity. So far, one randomised trial has been published among elderly subjects who were living in residential housing for senior citizens. In this trial a non-standard duration of PEP (6 weeks) was used and PEP could be initiated following detection of influenza in the vicinity of a home, making these data hard to extrapolate. The current lack of scientific evidence for effectiveness among high-risk groups such as nursing home residents is confirmed in a recent meta-analysis [13].

As observed before, timely implementation of antiviral medication can be a challenge [14]. Only half of the Dutch nursing homes managed to start oseltamivir within 48 h of the start of symptoms. Improved procedures, which would facilitate rapid laboratory diagnosis, will be instrumental in reducing this time span. Concerns on the need of many of the scarce financial resources has also been vouched in the UK [15], although a recent Canadian analysis observed that use of oseltamivir in nursing homes could be cost-effective [16].

Despite of the high vaccination coverage among residents of around 90%, influenza outbreaks occurred in a large number of nursing homes. Due to the continuous antigenic drift of the influenza virus, some mismatch between the vaccine and the circulating strains will usually occur. Unless the mismatch is considerable as occurred in the 2003/2004 season when the Fujian-like A(H3N2) virus circulated [17,18], a limited mismatch is unlikely to result in reduced vaccine efficacy. Among the elderly population, the immune response to vaccination is limited due to age-related decline in immune function, often compounded by specific immune-suppressive pathology. This can result in an average vaccine effectiveness among the elderly population of less than 50% [19]. If outbreaks occur late in the season, waning immunity further reduces the number op protected people. Also, vaccination coverage among staff was very low, and thus the overall vaccination coverage in many nursing homes may have only been around 50%.

The response rate to the questionnaire was 56%. When including the basic data obtained from the non-responders, 65% of Dutch nursing homes have been reached. It cannot be excluded that some selection bias has occurred. It is likely that among the non-responders fewer outbreaks have occurred, which may have led to an overestimation of the percentage of nursing homes suffering an outbreak. On the other hand, a third of the nursing homes that suspected an outbreak on clinical grounds, did not request laboratory testing to confirm this clinical diagnosis, which may have led to underestimation of the percentage of confirmed outbreaks. There is no reason to assume the non-responders would represent different opinions regarding the use of antivirals; which is supported by the fact that non-responders interviewed gave similar reasons as those who returned the questionnaire.

In conclusion, in view of the high risk among the frail nursing homes populations and the threat of a possible influenza pandemic, nursing homes should be encouraged to formulate an outbreak management plan well ahead of the expected season. At the same time, this study indicates that the major concerns with regards to the prescription of antivirals in nursing homes need to be addressed if antiviral medication is to play a central role in the control of influenza outbreaks in nursing homes.

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