

Influenza vaccination coverage in patients treated with chemotherapy: current clinical practice

M.L. Wumkes^{1*}, A.M.T. van der Velden¹, A.W.G. van der Velden², J.M.L. Stouthard³, M.R. Nijziel⁴, M. Westerman⁵, A. Beeker⁶, A. Meerveld-Eggink⁷, G.T. Rijkers⁸ D.H. Biesma⁷

¹Department of Internal Medicine, Tergooi Hospitals Hilversum, the Netherlands, ²Department of Internal Medicine, Martini Hospital Groningen, the Netherlands, ³Department of Internal Medicine, Maasstad Hospital Rotterdam, the Netherlands, ⁴Department of Internal Medicine, Maxima Medical Centre Eindhoven, the Netherlands, ⁵Department of Internal Medicine, Medical Centre Alkmaar, the Netherlands, ⁶Department of Internal Medicine, Spaarne Hospital Hoofddorp, the Netherlands, ⁷Department of Internal Medicine, St. Antonius Hospital Nieuwegein, the Netherlands, ⁸Department of Medical Microbiology and Immunology, St. Antonius Hospital Nieuwegein, the Netherlands, *corresponding author: tel.: +31 (0)88 7531753, fax: +31 (0)35 5391235, e-mail: Mwumkes@tergooi.nl

ABSTRACT

Background: Influenza virus vaccination is recommended for patients treated with chemotherapy. Little is known about vaccination coverage in these patients.

Methods: Vaccination coverage in the Netherlands was analysed by questionnaires completed by general practitioners, within a catchment area of 1.3 million people, in the period 2010-2011.

Results: Of 433 eligible adult patients treated with chemotherapy for breast or colorectal cancer, 144 patients gave permission for us to approach their general practitioner with a questionnaire. General practitioners were asked about vaccination coverage, awareness of recommendations and their opinion about the responsibility for vaccination. We received 114 (79%) completed questionnaires. Sixty-seven out of 114 patients (59%) were vaccinated against influenza. Forty-four (66%) of these patients also had an indication for vaccination based on age (age ≥ 60 years). According to 48% of the general practitioners, the responsibility for vaccination belongs to the competence of the treating medical oncologist.

Conclusion: Influenza vaccination coverage is limited to 59% of patients treated with chemotherapy. Guidelines for responsibility (general practitioner or medical oncologist) may increase the vaccination rate of cancer patients.

KEYWORDS

Chemotherapy, influenza virus vaccination, breast cancer, colorectal cancer, vaccination coverage

INTRODUCTION

Influenza viruses cause important epidemic infections with a potential risk of developing acute respiratory disease. Infection rates are highest in children, but morbidity and mortality are highest in various high-risk groups.¹ Among these groups are patients aged ≥ 60 years, patients with heart or lung diseases and patients with diminished immune function due to treatment with chemotherapy or other immunosuppressive drugs.² Patients receiving chemotherapy or immunosuppressive drugs have an impaired immune response to bacterial and viral infections and are therefore at risk of serious post-influenza complications.³ In the United States yearly 441 per 100,000 oncology patients are hospitalised due to influenza. This is 3-5 times higher than in the general population. The mortality rate is 9% in cancer patients with a relative risk of 4.0 in comparison with the general population.⁴ Therefore, yearly influenza vaccination is strongly recommended for patients with reduced function of the immune system due to treatment with chemotherapy or immunosuppressive drugs.²

Various factors influence the immune status and the response to immunisation in patients with cancer. First, the disease state can be directly immunosuppressive, in particular in patients with haematological malignancies. Second, treatment modalities for cancer can have (severe) immunosuppressive effects. Chemotherapy has its cytotoxic effects particularly on rapidly growing tumour cells, but the full functional capacity of the immune system also depends on rapid proliferation of cells and is therefore adversely affected.⁵

This negative effect of chemotherapy on immune function is, however, variable, depending on the chemotherapy regimen. Influenza virus vaccination in this group of patients is important to reduce the risk of serious complications of an influenza infection as well as to avoid potential risk of postponing the chemotherapy treatment due to infection. However, the immune response to the vaccine may be suboptimal because the protection conferred by immunisation is lower in immunosuppressed cancer patients.⁵

Despite the recommendations, vaccination coverage in high-risk patients can be improved. In the Netherlands, seasonal influenza vaccination is offered by the government free of charge to elderly and other risk groups and distributed through general practitioners (GPs).⁶ Influenza vaccine coverage in 2010-2011 was about 75% for adults aged ≥ 60 years as well as in patients with reduced immune function (patients with liver cirrhosis, asplenia, autoimmune diseases and patients treated with chemotherapy or other immunosuppressive drugs). Vaccine coverage of patients treated with chemotherapy as a separate risk group is unknown.⁷ Reasons given by physicians not to vaccinate their patients during chemotherapy are lack of awareness of the recommendations and concern about the efficacy of the influenza vaccination in patients with solid tumours treated with chemotherapy.³

The aim of this study was to evaluate GPs current practice with regard to influenza vaccination in patients treated with chemotherapy for breast cancer or colorectal cancer in the Netherlands.

PATIENTS AND METHODS

This study was conducted in patients treated with chemotherapy for breast cancer or colorectal cancer during the influenza period 2010-2011. Defining this patient group was considered to reflect a comprehensive picture of current practice, because breast cancer as well as colorectal cancer have high incidence and occur in patients with a relatively wide age range.

To identify patients the following strategy was used. Six non-academic teaching hospitals participated in this study (catchment area 1.3 million people). The principal investigators of each participating hospital were asked to register all adult patients treated with adjuvant or palliative chemotherapy for breast cancer or colorectal cancer during the influenza period of 2010-2011. Patients were then approached by letter and asked for written informed consent to contact their GP for completion of a questionnaire. The questionnaire consisted of questions concerning vaccination coverage of patients and their

informal carers, timing of vaccination and influence of chemotherapy regimen as well as the GP's opinion regarding the responsibility of the medical oncologist for instructions on influenza vaccination during chemotherapy. The questionnaire is shown in *appendix A*. A descriptive analysis has been carried out.

RESULTS

In the six participating hospitals, 433 patients were identified with breast cancer or colorectal cancer receiving treatment with chemotherapy in the influenza period of 2010-2011 (*figure 1*). A total of 418 patients were approached for informed consent, 35% responded. This percentage was approximately the same in each participating centre. Reasons for not participating were not obtained. Informed consent was given by 98% of the patients. A total of 141 GPs were approached and asked to complete the questionnaire of which 79% returned the questionnaire. Due to the fact that some patients had the same GP, a total of 107 different GPs participated in this study.

Vaccination

Of the 114 patients, 67 patients (59%) were vaccinated against influenza (*figure 2*). Of these patients, 66% already had an indication for vaccination based on age (age ≥ 60 years). Thirty-four patients' informal carers (30%) were vaccinated, two of them had no indication for influenza other than their partners' treatment with chemotherapy (*figure 3*).

Figure 1. Overview of inclusion and response

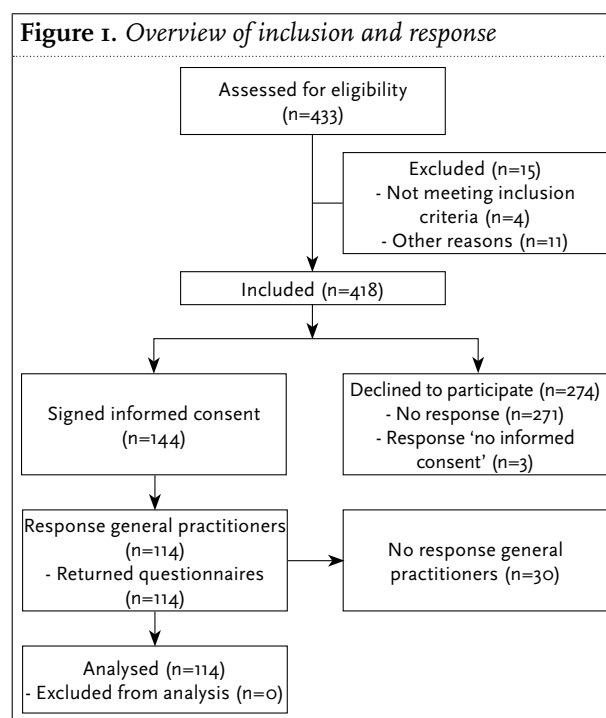


Figure 2. Vaccination status of patients treated with chemotherapy in proportions

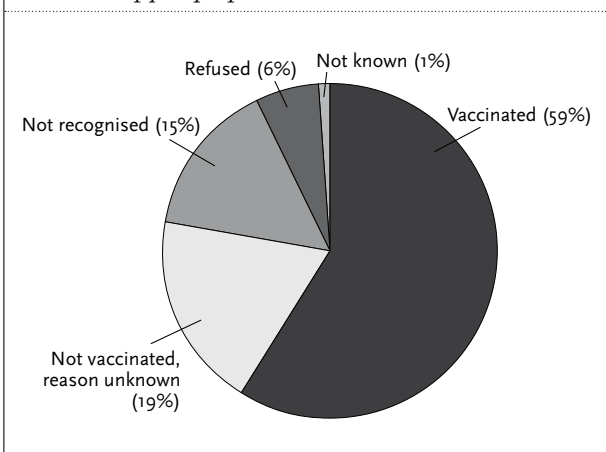
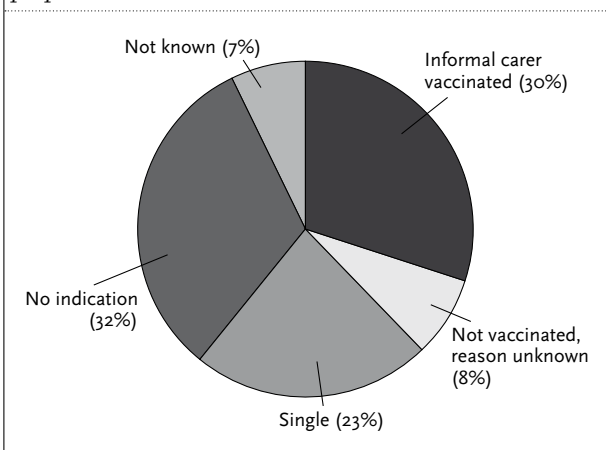


Figure 3. Vaccination status of informal carers in proportions



Information

During the influenza period of 2010-2011, 60% of the participating GPs were approached 1-5 times by a patient treated with chemotherapy for advice concerning influenza vaccination; 8% were consulted 6-10 times. This consultation was independent of the chemotherapy regimen or underlying malignancy. Of the GPs, 32% were not contacted at all.

Awareness of vaccination recommendations

Forty-nine of the participating GPs were not aware of the fact that yearly influenza vaccination is recommended in the national guidelines for all patients treated with chemotherapy or other immunosuppressive drugs. Of the GPs, 48% would not approach patients treated with chemotherapy and stated that vaccination against influenza is the responsibility of the treating medical oncologist.

One-third of the GPs actively approached patients treated with chemotherapy to provide an influenza vaccination, 18% approached their patients occasionally when they remembered to do so.

Fifty-two percent of the GPs indicated that their decision to provide an influenza vaccination to a patient treated with chemotherapy was not influenced by the chemotherapy regimen itself. On the contrary, 43% of the GPs stated that their decision was influenced by the chemotherapy and the degree of myelosuppression it causes. Only a small percentage (3%) consulted the treating medical oncologist.

Optimal timing of vaccination

The results regarding the optimal timing of influenza vaccination during chemotherapy are presented in *table 1*. One-third of the GPs would consult the treating medical oncologist or did not provide an answer to the question on what is known about the optimal timing of vaccination. The majority (94%) of the GPs are in need of more information about the efficacy and optimal timing in patients treated with chemotherapy.

DISCUSSION

We studied the current practice of GPs with regard to influenza vaccination in patients treated with chemotherapy for breast cancer or colorectal cancer in different parts of the Netherlands. It should be emphasised that this issue is not only relevant in the Netherlands but worldwide.

Limitations of the study

The main limitation of the study is the low response rate of patients. Two-thirds of the identified patients did not respond for reasons that are unknown. Patients were not approached by a clinician but by letter which could have influenced the response in a negative way. The low response rate might have led to a representation bias: patients who were not interested in participating in this study might also not be aware of the risks associated with their immunocompromised state. It is also possible that patients not responding were already vaccinated and

Table 1. GPs opinion on optimal timing of vaccination during chemotherapy (n=GPs)

Optimal timing of vaccination	Frequency (n)	(n) %
Before the next dose of chemotherapy	25	23
Two weeks after the last regimen	26	24
Not useful to vaccinate, no serological response	17	16
Other	39	37
Total	107	100

informed about the risks and therefore did not feel the need to participate.

Furthermore, 21% of GPs did not return the questionnaire. Potentially their proportion of vaccination coverage is lower than those who actually responded.

In the Netherlands, vaccine coverage in 2010-2011 was 75% for patients with a reduced immune function. No distinction was made between the different groups of patients with a reduced immune state, therefore the vaccine coverage in patients treated with chemotherapy is not known.⁷ In this study of 114 Dutch patients vaccination coverage was 59%. Since two-thirds of these patients already had an indication for vaccination based on age (age ≥ 60 years), it is difficult to determine how many patients were vaccinated because they were receiving chemotherapy.

Awareness of the recommendations

Almost 50% of the participating GPs were not aware of the fact that yearly influenza vaccination is recommended in the national guidelines for all patients treated with chemotherapy or other immunosuppressive drugs independently of the chemotherapy regimen or the degree of immunosuppression it causes.² Scarce available data about the efficacy and optimal timing of influenza vaccination in this high-risk group might be an explanation. Despite the guidelines, 40% did not receive the vaccination; of these patients 37% were not identified as eligible for influenza vaccination by a computerised search on ICPC (International Classification of Primary Care) codes. Since there is no ICPC code for treatment with chemotherapy, these patients are not automatically selected. The other 60% were identified as eligible for influenza vaccination by an ICPC code based on age or other comorbidity.

The development of an ICPC code for treatment with chemotherapy could lead to identification of this high-risk group and therefore improve vaccination coverage. However, patient records need to be accurately documented by the GPs to succeed.

Regarding the relatively low vaccination coverage of the patients' carers, routine vaccination of informal carers of a patient treated with chemotherapy is not recommended in the Netherlands. A GP may decide to vaccinate informal carers if considered necessary, but the vaccine will not be covered by health insurance.² Therefore, it is not surprising that informal carers without an indication of their own are not vaccinated.

Optimal timing of vaccination

Limited recent data are available on the optimal timing and efficacy of influenza vaccination while receiving ongoing chemotherapy treatment.

Vilar-Compte *et al.* showed that during chemotherapy, 183 patients with breast cancer indeed had a lower response to vaccination than patients who did not receive chemotherapy.⁸ Brydak *et al.* found that immune response to influenza vaccination in breast cancer patients with or without chemotherapy was as effective as vaccination of healthy adults. The patient group, however, was very small (n=9) and heterogeneous.³

In our study, the GPs have various opinions on the optimal timing of vaccination. This is expected because of the absence of specific guidelines and the limited recent data available on the optimal timing of vaccination. In general it is advised to vaccinate patients before starting chemotherapy.^{9,10} Because the seasonal influenza vaccination campaign is restricted to the months October and November, it is not always possible to administer the vaccine before the start of the chemotherapy. Ortals *et al.* vaccinated oncology patients on the day of chemotherapy or at the time of their white blood cell count nadir. Only 50% of the patients achieved seroconversion on the day of chemotherapy, whereas 93% of the patients vaccinated in their nadir showed an adequate antibody response. This study, which was conducted in 1977, still forms the basis of current recommendations. It should be noted that the Ortals study only included a very limited number of patients with breast cancer (n=11),¹¹ (reviewed by Pollyea *et al.*). Most of the other influenza vaccination studies in cancer patients were performed in the 1970s and 1980; over the years considerable changes have been made in vaccine formulations and chemotherapy regimens.

During the influenza vaccination period in 2009, we conducted a pilot study in patients with breast cancer (Meerveld-Eggink *et al.*) Breast cancer patients received influenza vaccination during 5-fluorouracil, epirubicin and cyclophosphamide (FEC)-containing chemotherapy regimens. Thirty-eight patients were randomised for early (day 4) or late (day 16) vaccination during the chemotherapy cycle.

In this pilot study, patients vaccinated at day 4 tended to reach higher antibody levels compared with patients vaccinated at day 16.¹³ Studies with larger patient numbers have to be conducted to confirm this effect.

Responsibility

Of the GPs, 48% did not approach patients receiving chemotherapy because in their perspective it is the responsibility of the treating medical oncologist that their patient is vaccinated against influenza. In the Netherlands, the influenza vaccine is issued to GPs by the government and the GPs are primarily responsible for administering a vaccine to every eligible patient. However, in our study GPs considered it the medical oncologist's responsibility to vaccinate patients undergoing chemotherapy treatment.

Since the awareness of the indication for vaccination, in combination with specific knowledge on the immune suppressive effects of the anti-cancer treatment, might be greater among medical oncologists, we believe that medical oncologists should identify patients eligible for vaccination.

The high response rate of the GPs (79%), the high percentage of GPs in need of more information about the efficacy, optimal timing and recommendations, as well as the high number of patients consulting the GP for advice indicate that influenza vaccination is a timely topic and that further studies have to be conducted to achieve more information in order to establish (inter)national guidelines.

In conclusion, vaccination coverage in patients treated with chemotherapy in the Netherlands can be improved. Different strategies towards improvement of vaccination coverage could be developed. We suggest better education and information for GPs.

Further studies have to be conducted to assess the optimal timing of vaccination during chemotherapy. Medical oncologists should be encouraged to actively inform the GP about the need for influenza vaccination of their individual patients. A national campaign might improve the vaccination coverage in this high-risk group.

ACKNOWLEDGEMENTS

We thank all patients and general practitioners for their participation in this study.

Grant support: not applicable. There is no conflict of interest.

REFERENCES

1. Fiore A, Shay D, Haber P, et al. Prevention and control of influenza. Recommendation of the Advisory Committee on Immunization Practices (ACIP) 2008. *MMWR Recomm Rep*. 2008; 57:1-60.
2. Health Council of the Netherlands. Influenza vaccination: revision of the indication. The Hague: Health Council of the Netherlands, 2007; publication no.2007/09E. ISBN 978-90-5549-712-6.
3. Brydak L, Guzy J, Starzyk J, Machala M, Gózdź S. Humoral immune response after vaccination against influenza in patients with breast cancer. *Support Care Cancer*. 2001;9:65-8.
4. Cooksley C, Avritscher E, Bekele B, Rolston K, Geraci J, Elting L. Epidemiology and outcomes of serious influenza-related infections in the cancer population. *Cancer*. 2005;104:618-28.
5. Arrowood J, Hayney M. Immunization recommendations for adults with cancer. *Ann Pharmacother*. 2002; 36:1219-29.
6. Van Essen G, Bueving H, Voordouw A, et al. NHG-Standaard Influenza en influenzavaccinatie, Eerste herziening. *Huisarts Wet*. 2008;51:1-12 (<http://nhg.artsennet.nl/>).
7. Jansen B, Tacken M, Mulder J, Visscher S, Tiersma W, Brasspenning J. Scientific institute for quality of health care. Monitoring vaccine coverage national program flu prevention 2011. ISBN:978-90-76316-41-3.
8. Vilar-Compte D, Cornejo P, Valle-Salinas A, et al. Influenza vaccination in patients with breast cancer: a case-series analysis. *Med Sci Monit*. 2006;12:CR332-CR336
9. Sommer A, Wachel B, Smith J. Evaluation of vaccine dosing in patients with solid tumors receiving myelosuppressive chemotherapy. *J Oncol Pharm Pract*. 2006;12:143-54.
10. Melcher L. Recommendations for influenza and pneumococcal vaccinations in people receiving chemotherapy. *Clin Oncol (R Coll Radiol)*. 2005;17:12-5.
11. Ortals D, Liebhaber H, Presant C, Van Amburg III A, Lee J. Influenza immunization of adult patients with malignant diseases. *Ann Intern Med*. 1977;87:552-7.
12. Pollyea D, Brown J, Horning S. Utility of Influenza Vaccination for Oncology Patients. *J Clin Oncol*. 2010; 28:2481-90.
13. Meerveld-Eggink A, de Weerd O, van der Velden AMT, et al. Response to influenza virus vaccination during chemotherapy in patients with breast cancer. *Ann Oncol*. 2011;22:2031-35.

APPENDIX A – QUESTIONNAIRE

1. During last influenza season (2010-2011), was the influenza vaccine administered to the patient mentioned above?
 - a. Yes
 - b. No, reason:

2. Did the informal carers of the patient mentioned above get vaccinated with the influenza vaccine?
 - a. Yes
 - b. No, reason:

3. Do you (actively) approach patients who are treated with chemotherapy during the influenza season to get vaccinated against influenza?
 - a. Yes
 - b. No, responsibility of oncologist
 - c. Sometimes, reason:

4. Does the chemotherapy regimen and the degree of myelosuppression it causes influence your decision to administer the influenza vaccine?
 - a. Yes
 - b. No

5. During last influenza season (2010-2011), were you consulted frequently by patients with a malignancy for advice regarding influenza vaccination ?
 - a. Yes, approximately:times
 - b. No, approximately:.....times

6. In your opinion, what is the optimal timing of influenza vaccination in patients on chemotherapy?
 - a. Just before the next chemotherapy cycle
 - b. Two weeks after the last gift of chemotherapy
 - c. Do not administer the vaccine when on treatment with chemotherapy, there will not be an adequate (serological) response
 - d. Differently, explanation:

7. Would you like more information about the optimal timing of vaccination in this patient category?
 - a. Yes
 - b. No

8. In your opinion, is this subject relevant?
 - a. Yes
 - b. No, reason: