RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU
NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT

RIVM report 217617 001

Surveillance of acute respiratory infections in general practices - The Netherlands, winter 1997/98

M.L.A. Heijnen[1], A.I.M. Bartelds[2], B. Wilbrink[3],
C. Verweij[3], K. Bijlsma[3], H. van der Nat[3], H. Boswijk[3],
A.S. de Boer[1], M.J.W. Sprenger[1], J.W. Dorigo-Zetsma[3]

October 1999

[1] RIVM - Department of Infectious Diseases Epidemiology (CIE)
[2] Netherlands Institute of Primary Health Care (NIVEL)
[3] RIVM - Diagnostic Laboratory for Infectious Diseases and Perinatal Screening (LIS)

M.L.A. Heijnen	data analysis, report writing
A.I.M. Bartelds	co-ordination sentinel surveillance network
B. Wilbrink	co-ordination molecular analysis
C. Verweij, K. Bijlsma	viral culture
H. van der Nat, H. Boswijk	PCR-analyses
A.S. de Boer	critical review of the report
M.J.W. Sprenger	project leader
J.W. Dorigo-Zetsma	co-ordination laboratory work, contribution to report

This investigation has been performed by order and for the account of the Health Care Inspectorate, within the framework of project V/217617/01, Respiratory infections: surveillance and epidemiology.

ISSN number: 1566-5941

RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Abstract

To provide insight into the virological aetiology of influenza-like illnesses and other acute respiratory infections, nose/throat swabs were taken by 30 general practitioners of the sentinel surveillance network of the Netherlands Institute of Primary Health Care from a random selection of patients seen for such infections in their consultancies during the 1997/98 winter. The swabs were analysed at the National Institute of Public Health and the Environment for respiratory viruses, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* using viral culture and polymerase chain reaction (PCR) analysis. At least one respiratory pathogen was detected in 52% of the 363 swabs. The most frequently detected virsues were influenza, mainly A(H3N2), and rhinoviruses, occurring in 23% and 21% of the swabs, respectively. Rhinoviruses predominated from September to December 1997, whereas influenza viruses prevailed from January to April 1998. Forty-five percent of respiratory pathogens (74% of the rhinoviruses and 86% of the enteroviruses and respiratory syncytial viruses) were detected by PCR analysis only. Influenza virus was isolated six times more often in swabs from patients with an influenza-like illness (i.e. in 30%) than in swabs from patients with another acute respiratory infection. In 23% of the patients with influenza-like illness, however, respiratory pathogens other than influenza were detected and in 46% no micro-organisms were detected. Results were compared with those of the five previous winters. Insight into virological aetiology of acute respiratory infections obtained through this surveillance (the only one in the Netherlands carried out among general-practice patients) can contribute to effective prevention and control of such infections. Suggestions to improve the surveillance are offered.

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Samenvatting

Sinds 1970 registreren huisartsen van het peilstationnetwerk van het Nederlands Instituut voor Onderzoek van de Gezondheidszorg (NIVEL) patiënten die hen consulteren vanwege een influenza-achtig ziektebeeld (IAZ) om gedurende de winter wekelijks de IAZ-incidentie te berekenen. Om inzicht te verschaffen in de virologische etiologie van IAZ en andere acute respiratoire infecties neemt sinds winter 1992/93 circa 75% van de peilstationartsen neus- en keelwatten af bij een random selectie van patiënten die hen consulteren vanwege dergelijke infecties. Deze monsters worden op het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) geanalyseerd op respiratoire virussen, *Chlamydia pneumoniae* en *Mycoplasma pneumoniae* met behulp van viruskweek en PCR.

In winter 1997/98 stuurden 30 huisartsen 363 monsters naar het RIVM; 69% van deze monsters waren afkomstig van IAZ-patiënten. In 52% van de monsters werd tenminste één luchtwegpathogeen gedetecteerd; in 5% van de monsters werden twee micro-organismen aangetroffen. Influenzavirussen, voornamelijk type A(H3N2), en rhinovirussen werden het vaakst aangetoond, nl. in respectievelijk 23% en 21% van de monsters. Rhinovirussen circuleerden m.n. van september tm. december 1997 en influenzavirussen domineerden van januari tm. april 1998. Vijfenveertig procent van de luchtwegpathogenen (74% van de rhinovirussen en 86% van de enterovirussen en respiratoir syncytieel virussen) werd alleen door PCR-analyse gedetecteerd.

Influenzavirus werd zes keer zo vaak geïsoleerd uit monsters van IAZ-patiënten (in 30% daarvan) dan uit monsters van patiënten met een andere acute luchtweginfectie. Bij 23% van de IAZ-patiënten werd echter een ander luchtwegpathogeen dan influenzavirus aangetoond en bij 46% werd geen micro-organisme gevonden. De IAZ-registratie kwam redelijk goed overeen met de isolatie van influenzavirussen. Het was een relatief laat en mild influenzaseizoen: IAZ-incidentie was maximaal 17 per 10.000 personen per week. Gedurende de hele winter was de IAZ-incidentie hoger bij kinderen van 0 tot 4 jaar dan bij patiënten ouder dan 4 jaar. Ook in de virologische etiologie werden verschillen gevonden tussen leeftijdscategorieën. Er is een schatting gemaakt van de incidentie van influenzavirusinfectie in de algemene bevolking op basis van de IAZ-registratie en de isolatie van influenza-virussen.

Het inzicht in virologische etiologie van acute respiratoire infecties inclusief IAZ op basis van deze surveillance, de enige onder huisartspatiënten, kan een bijdrage leveren aan effectieve preventie en controle van dergelijke infecties. Er worden suggesties gedaan ter verbetering van de surveillance.

Summary

Since 1970 general practitioners of the sentinel surveillance network of The Netherlands Institute of Primary Health Care (NIVEL) register patients consulting them for influenza-like illnesses (ILI) to calculate the ILI incidence weekly during the winter. To provide insight in the virological aetiology of influenza-like illnesses and other acute respiratory infections, circa 75% of the general practitioners takes nose/throat swabs from a random selection of patients consulting them for such infections since winter 1992/93. These swabs are analysed at the National Institute of Public Health and the Environment (RIVM) for respiratory viruses, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* by viral culture and polymerase chain reaction (PCR).

In winter 1997/98, 30 general practitioners sent 363 swabs to RIVM; 69% of these swabs were obtained from ILI patients. At least one respiratory pathogen was detected in 52% of the swabs; in 5% of the swabs two micro-organisms were detected. Influenza viruses, mainly A(H3N2), and rhinoviruses were detected most frequently, i.e. respectively in 23% and 21% of the swabs. Rhinoviruses predominated from September until December 1997, whereas influenza viruses prevailed from January until April 1998. Forty-five percent of respiratory pathogens (74% of the rhinoviruses and 86% of the enteroviruses and respiratory syncytial viruses) were detected by PCR analysis only.

Influenza virus was isolated six times more often in swabs from patients with influenza-like illness (i.e. in 30%) than in swabs from patients with another acute respiratory infection. In 23% of the patients with influenza-like illness, however, respiratory pathogens other than influenza were detected and in 46% no micro-organism was detected. ILI registration was reasonably consistent with influenza virus isolations. It was a relatively late and mild influenza season: ILI incidence never exceeded 17 per 10,000 persons per week. Throughout the winter, ILI incidence was higher in children age 0 to 4 years than in patients aged 4 years or over. Differences by age were found in virological aetiology, too. Incidence of influenza virus infection in the general population was estimated based on ILI registration and influenza virus isolations.

Insight in virological aetiology of acute respiratory infections obtained by this surveillance, the only one among general practice patients, can contribute to effective prevention and control of such infections. Suggestions are given to improve the surveillance.

Abbreviations

ARI	acute respiratory infection(s)
EC	European Community
EISS	European Influenza Surveillance Scheme
EUR	Erasmus University Rotterdam
GP	general practitioner or general practice
HSV	herpes simplex virus
ILI	influenza-like illnesses
m.o.	micro-organism
NIVEL	Netherlands Institute of Primary Health Care
PCR	polymerase chain reaction
positive swab	nose/throat swab in which at least one m.o. other than HSV was detected
RIVM	National Institute of Public Health and the Environment
RSV	respiratory syncytial virus

1. Introduction and reading guide

This report describes the methods and results of the yearly NIVEL/RIVM surveillance of acute respiratory infections (ARI; including influenza-like illnesses (ILI)) in general practitioner (GP) patients for winter 1997/98. This surveillance is currently carried out in the framework of RIVM project no. V/217617/01 "Respiratory infections: surveillance and epidemiology" and formerly in the framework of RIVM project no. 245607 and 243614.

To bring the reporting on the NIVEL/RIVM surveillance of ARI under the attention of more people than in previous years, the main results of winter 1997/98 are published in *Eurosurveillance*. *Eurosurveillance* is a journal that reports on the epidemiology of infectious diseases in the European Community (EC) and is distributed among 11.000 people working on public health in the EC.

This report consists of four parts: (1) this introduction and reading guide, (2) the main results as published in *Eurosurveillance,* (3) the remaining results, and (4) concluding remarks and recommendations.
The *Eurosurveillance* article (**chapter 2**) describes the background, aim, methods, main results and short discussion of the surveillance. It is recommended to read this part to get a quick overview of the methods and main results of the surveillance.
More detailed results can be found in **chapter 3** where the remaining results are presented as tables and figures plus a short discussion. First, the distribution of the number of swabs received during the winter period 1997/98 is discussed (figure 3.1-3.4). Then the age distribution of the patients of which swabs were obtained is compared with the age distribution of the Dutch general population (figure 3.5). Subsequently, in addition to table 1 and figure 1 and 2 from part 2, the micro-organisms (m.o.) that were detected are described separately for patients registered with influenza-like illness (ILI) and patients not registered with ILI (table 3.2 and 3.3, figure 3.8). The m.o. detected are compared with those in previous winters (table 3.1 and 3.4, figure 3.6 and 3.7). In addition to figure 5 of part 2, the age distribution of the patients in whose swabs influenza virus, rhinovirus or RS-virus was detected (figure 3.9 and 3.10), and multiple infections are discussed (table 3.5 and 3.6). Next, in addition to figure 3 and 4 and the comparison with other European countries in part 2, the influenza season 1997/98 is described, the incidence of influenza virus infection is estimated by combining ILI registration and influenza virus detection rates by age group (table 3.7-3.10, figure 3.11-3.14), degree of urbanisation (table 3.11-3.13) and region (table 3.14-3.16). Information on influenza vaccination and symptoms of ARI and ILI patients will be reported elsewhere. Characterisation of the influenza viruses isolated from the nose/throat swabs of the GP-patients described in this report and of isolates from hospital patients is carried out at the Erasmus University Rotterdam (EUR) and described by Claas *et al.*[1].
In **chapter 4**, the strengths and weaknesses of this surveillance are discussed and suggestions for the continuation of the surveillance are made.

In the beginning of winter 1997/98, a letter of alert was sent to the NIVEL sentinel general practices (**Appendix II**; in Dutch). Each nose-throat swab was accompanied by a form asking for information about the patient and the illness (**Appendix III**; in Dutch). The results of the surveillance were presented at the European Society of Clinical Virology (ESCV) in Rotterdam, January 1999 and at the Dutch Society of Medical Microbiology (NVMM) in Veldhoven, April 1999 (**Appendix IV**). Other forms of reporting on this surveillance are described in **Appendix V**.

2. Main results as published in Eurosurveillance 1999;4(7/8):81-84

Surveillance of respiratory pathogens and influenza-like illnesses in general practices - The Netherlands, winter 1997/98

MLA Heijnen[1], JW Dorigo-Zetsma[2], AIM Bartelds[3], B Wilbrink[2] and MJW Sprenger[1]

[1]Department of Infectious Diseases Epidemiology (CIE), Bilthoven, The Netherlands
[2] Diagnostic Laboratory for Infectious Diseases and Perinatal Screening (LIS), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[3]Netherlands Institute of Primary Health Care (NIVEL), Utrecht, The Netherlands

Introduction

The Netherlands Institute of Primary Health Care (NIVEL) has coordinated the activities of a sentinel surveillance network of 43 general practices since 1970. These practices care for 1% of the Dutch population, a sample representative of the national population in terms of age, sex, and degree of urbanisation (1). NIVEL uses data from the network to calculate the incidence of influenza-like illness each week during the winter season. At the request of NIVEL, the system has been enhanced since the winter of 1992/93 by the National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu - RIVM), to include virus isolation and detection from nose/throat swabs obtained from patients with acute upper respiratory tract infections (ARI), of which on average influenza-like illness accounts for about 62%. This article presents the main findings of the surveillance of influenza-like illness and other ARI in general practice in the Netherlands in the winter of 1997/98, assesses the relationship between influenza virus isolation and registration with influenza-like illness, and compares virus isolation and polymerase chain reaction (PCR) analysis for respiratory syncytial virus (RSV), rhinovirus, and enterovirus.

Methods

The general practitioners in the NIVEL sentinel network registered patients who consulted them for influenza-like illness between week 40 in 1997 (beginning 29 September) and week 20 in 1998 (ending 17 May). The criteria for influenza-like illness were: acute onset (a prodromal stage of no more than 4 days), rectal temperature of at least 38°C, and at least one of the following symptoms (cough, coryza, sore throat, frontal headache, retrosternal pain, myalgia) (1). The NIVEL general practitioners were asked to take nose/throat swabs from patients who consulted them for ARI (including influenza-like illness), but excluding otitis and sinusitis. ARI was defined as a respiratory illness with an acute onset and at least one of the above mentioned symptoms. Each practice was asked to take at random a maximum of two swabs per week. The swabs were sent in GLY virus transport medium (2) to RIVM by post. At RIVM the swabs were registered by date of sampling and subjected to virus culture and PCR. tMK cells (tertiary cynomolgus monkey kidney cells) and GaBi cells (human diploid fibroblast cells) were used for virus culture and viruses were identified using standard procedures (3). PCR was performed for RSV (4), rhinovirus and enterovirus (5), *Mycoplasma pneumoniae* (6), and *Chlamydia pneumoniae* (7). We chose to look for viruses and *M. pneumoniae* and *C. pneumoniae* but not for bacteria because it has been estimated that 70% of all ARI in the community is caused by viruses and only 8% by bacteria (8). In the winter of 1996/97 some of the swabs were analysed for bacteria too: in only 9% of the swabs was a bacterium the only potentially pathogenic microorganism detected (9).

Results

During the winter of 1997/98, general practitioners from 30 (70%) of the sentinel practices provided RIVM with 363 nose/throat swabs from patients with ARI. These 30 sentinel practices were representative of all 43 practices in the network in terms of region, degree of urbanisation, and age and sex of patients. Swabs were taken during a period of 44 weeks: from week 36 in 1997 (beginning 1 September) till week 27 in 1998 (ending 5 July). At least one potentially pathogenic microorganism was detected in 52% (187 of 363) of the swabs (table) and in 5% (17 of 363) of the swabs two microorganisms were detected. Influenza viruses were detected most often (83 of 363, 23% of the swabs), followed by rhinoviruses (76 of 363, 21% of the swabs) (figure 1). Seventy-six of the influenza viruses were of the $A(H_3N_2)$ type; six influenza B viruses and one influenza $A(H_1N_1)$ virus were also isolated. Rhinoviruses predominated from September until December 1997, whereas influenza viruses prevailed from January until April 1998 (figure 2). Forty-five per cent (91 of 201) of respiratory pathogens (74% of the rhinoviruses and 86% of the enteroviruses and RSV) were detected by PCR only (table 1).

Influenza virus was isolated six times more often in swabs from patients registered with influenza-like illness than in swabs from patients registered with ARI but not influenza-like illness (figure 1). In 23% of the patients registered with influenza-like illness, however, respiratory pathogens other than influenza virus were detected and in 46% no microorganism was detected. Detection of a rhinovirus was twice as likely in swabs from ARI patients without influenza-like illness than in swabs from patients with influenza-like illness.

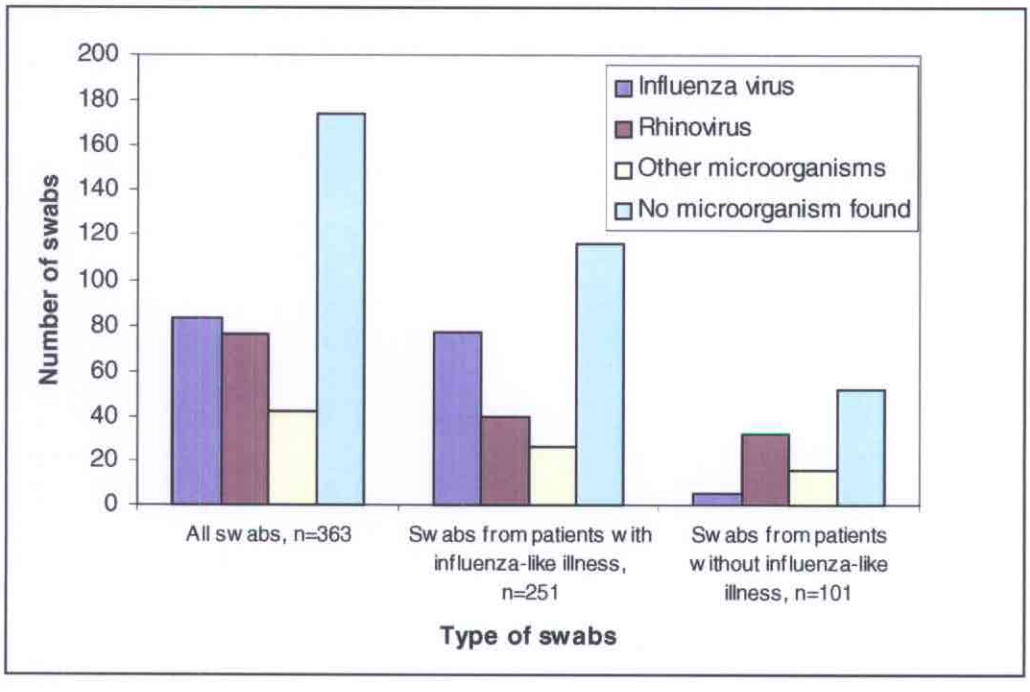

Figure 1 Potentially pathogenic microorganisms detected in nose/throat swabs from patients with acute upper respiratory tract infections: The Netherlands, winter 1997/98. Two swabs in which only herpes simplex virus (HSV) was detected were classified as 'no microorganism found' because HSV is not likely to cause respiratory symptoms in immunocompetent people

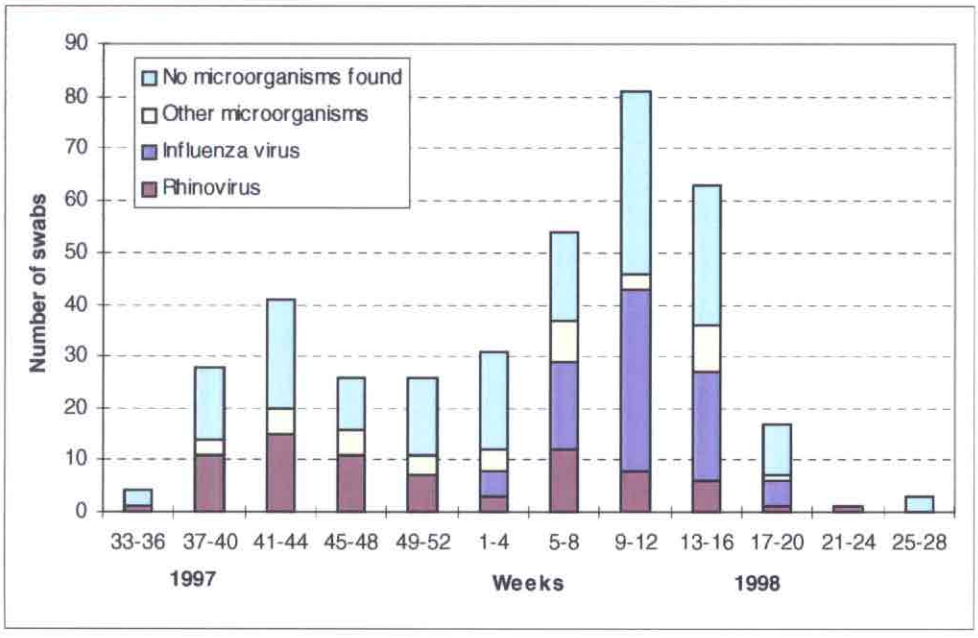

Figure 2 *Influenza viruses, rhinoviruses and other microorganisms detected in 363 nose/throat swabs from patients with an acute upper respiratory tract infection: The Netherlands, winter 1997/98. Two swabs in which only herpes simplex virus (HSV) was detected were classified as 'no microorganism found' because HSV is not likely to cause respiratory symptoms in immunocompetent people.*

Table 1 *Potentially pathogenic microorganisms detected in nose/throat swabs from patients with an acute respiratory infection, The Netherlands, winter 1997/98 (n=363)*

Microorganism	Number by culture	Number by PCR	Total number	Total detected as percentage of all submitted swabs	Total detected as percentage of all micro-organisms detected
Influenza virus	83		83	23	41
Rhinovirus	20	76	76	21	38
M. pneumoniae		16	16	4	8
Enterovirus	2	14	14	4	7
RSV	1	7	7	2	3
Adenovirus	2		2	0.6	1
Parainfluenza virus	2		2	0.6	1
C. pneumoniae		1	1	0.3	0.5

Herpes simplex virus (HSV) was isolated from five swabs. In three of these swabs another microorganism was detected, too. Since HSV is not likely to cause respiratory symptoms in immunocompetent people, the two swabs in which HSV only was detected were classified as 'no microorganism detected'.

Registration of influenza-like illness and isolation of influenza viruses from patients with influenza-like illness were reasonably in accordance with each other: the peak in influenza-like illness appeared four weeks after the peak in influenza virus isolates and a second peak in influenza virus isolates appeared one week after the peak in influenza-like illness (figure 3). A similar pattern was found when the numbers of isolates were expressed as percentage of the numbers of swabs received (data not shown).

Throughout the winter, the incidence of influenza-like illness was higher in children aged 0 to 4 years than in patients aged 4 years or over (figure 4). The percentage of swabs in which a microorganism was detected decreased with age (figure 5). Influenza virus was detected in about 40% of swabs from children aged 0 to 14 years. Rhinovirus was most frequently detected in swabs from patients aged 0 to 4 and 15 to 44 years (figure 5).

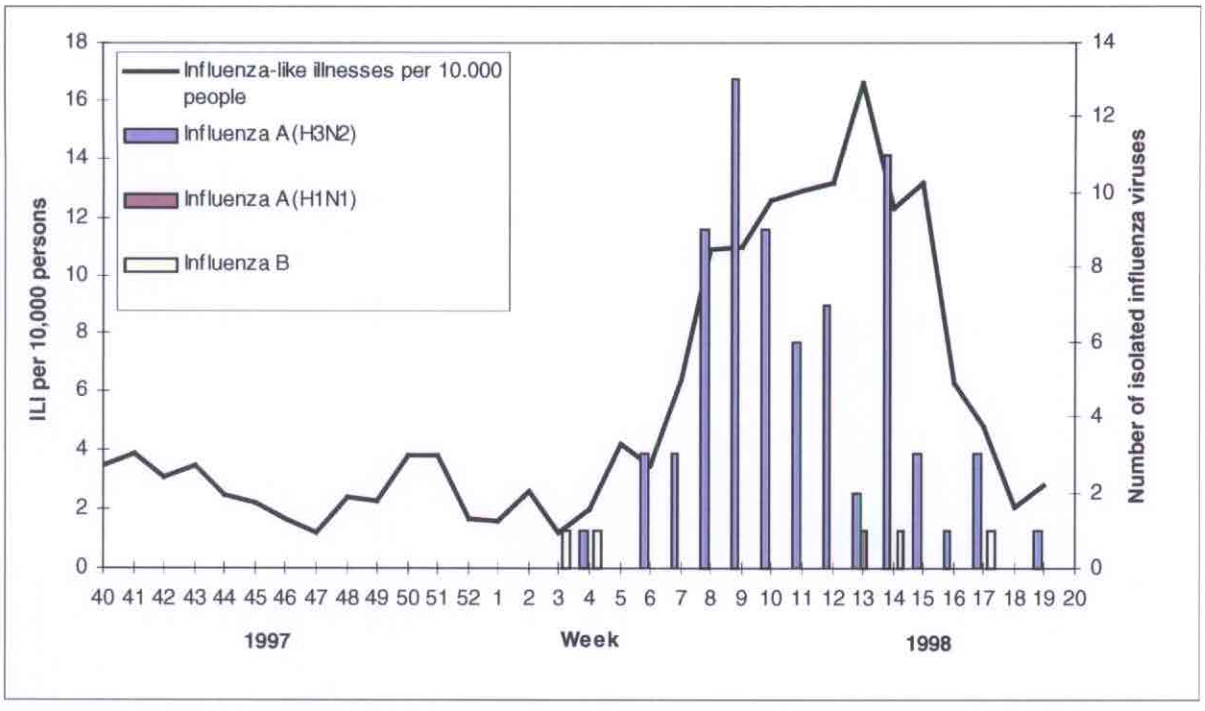

Figure 3 Influenza-like illnesses registered and isolates of influenza virus (n=77) from nose/throat swabs (n=251): The Netherlands, winter 1997/98

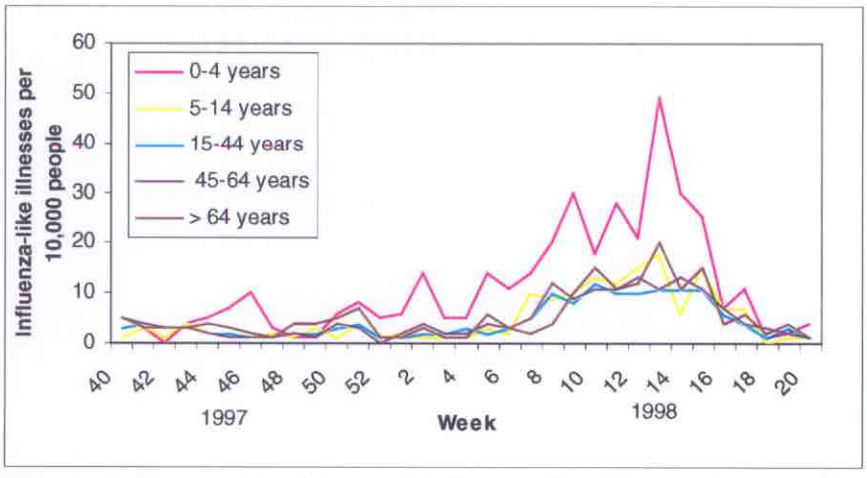

Figure 4 Reported incidence of influenza-like illnesses by age and week: The Netherlands, winter 1997/98

Discussion

The distribution of the various microorganisms detected is comparable with the findings in previous winters (9-13). Inability to detect a microorganism in 48% of the swabs may be due to swabs being taken too late for the microorganism to be present or viable, a non-infectious cause of the symptoms (such as allergy), the limited number of microorganisms sought, and limited sensitivity of the detection methods used.

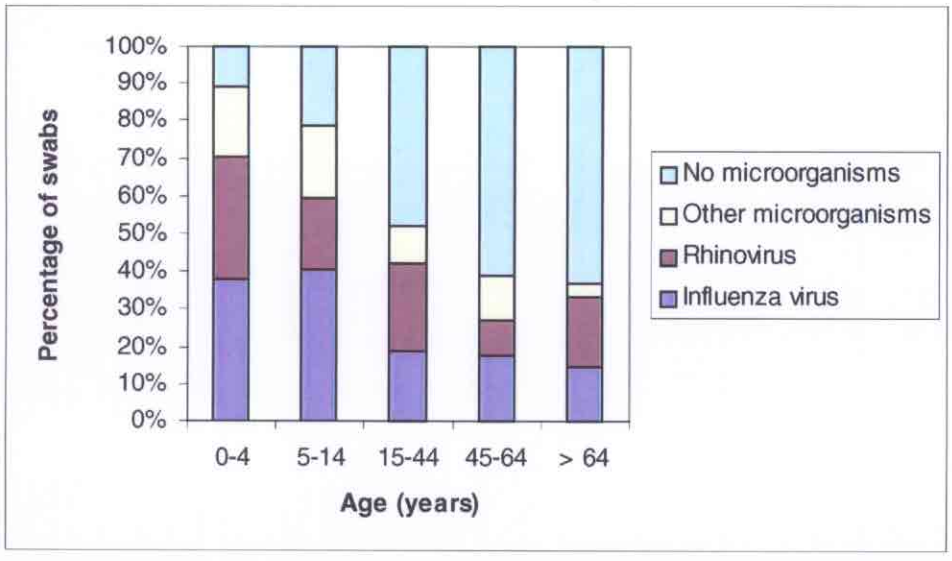

Figure 5 Microorganisms detected in 363 nose/throat swabs from patients with acute respiratory infection by age category: The Netherlands, winter 1997/98

Compared with previous winters (9-13), the influenza season in the Netherlands started late in winter 1997/98 and was of moderate intensity. The short lag in the peak of influenza-like illness behind that of influenza virus isolations was also seen in winters 1996/97, 1995/96, and 1993/94 (9,10,12). This delay may be because sentinel practices register relatively more cases of influenza-like illness once influenza virus is reported to be circulating. The second (smaller) peak of influenza virus isolations shortly after the influenza-like illness peak may have occurred because the sentinel practices sent in more influenza-containing swabs once they became aware that influenza virus was circulating. In winters 1994/95 and 1992/93 peaks in influenza virus isolation and influenza-like illness occurred at the same time (11,13).

In other European countries, the influenza season 1997/98 was relatively mild and late as well (14). In most countries influenza A(H_3N_2) virus dominated, except in England and Wales where influenza A(H_3N_2) and A(H_1N_1) viruses co-circulated (14,15). In Germany influenza A(H_1N_1) virus was isolated sporadically too (16). Influenza B virus was isolated sporadically in France and Germany (14,16).

PCR was more sensitive than viral culture for rhinoviruses, enteroviruses, and RSV. The difference may be attributable to delay caused by the postal regulations, especially for labile viruses such as RSV, which may be nonviable by the time a swab arrives at the laboratory. PCR can detect viruses that do not grow in cell culture (5), but little is known about how long viral RNA can be detected by PCR after an infection. One month after the first swab, seven out of 19 follow up swabs from people who still had symptoms but only one out of 25 follow

up swabs from people who had recovered were still positive for rhinovirus, enterovirus, or RSV by PCR (9). Thus, interpretation of a positive PCR result should take the patient's medical history into account.

Acknowledgements
The authors thank the general practitioners from the NIVEL sentinel network for registering ILI and taking nose/throat swabs; K. Bijlsma, C. Verweij, H. van der Nat, and H. Boswijk (RIVM) for laboratory analyses; M. Heshusius-van Valen (NIVEL) for administrative support, and A.S. de Boer (RIVM) for critical review of the manuscript.

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3. More detailed results

3.1 Number of swabs

The GP's of the NIVEL sentinel practices were asked to send in nose/throat swabs from patients who consulted them for ARI, with the following requests: (a) swabs from Monday through Thursday and a maximum of two swabs per week for logistic reasons, (b) swabs at random (preferably second ARI patient on Tuesday and second ARI patient on Wednesday), and (c) from 1 September 1997 onwards (Appendix II).
Between week 36 in 1997 (beginning 1 September) and week 27 in 1998 (ending 5 July) 363 nose/throat swabs from ARI patients were sent in by GP's of 30 (70%) of the 43 sentinel practices registering ILI. The 30 swab-taking practices were representative of all 43 practices in the network in terms of region and degree of urbanisation (figure 3.1 and 3.2). Sixty-nine percent (n=251) of the swabs were from patients registered with ILI and 28% (n=101) from patients not registered with ILI. From 11 patients (3%) the ILI status was unknown.

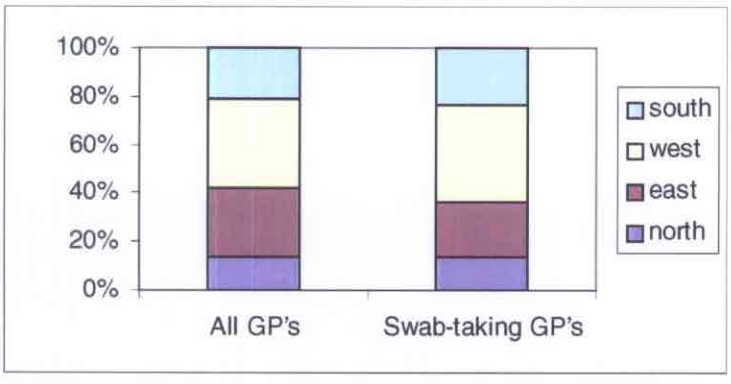

Figure 3.1 Distribution over the four regions in the Netherlands of the 43 general practices (GP) of the Netherlands Institute of Primary Health Care (NIVEL) registering influenza-like illness and of the 30 GP's of the NIVEL taking swabs from patients who consulted them for an acute respiratory infection, winter 1997/98

Compared with recent years we received fewer swabs (table 3.1). This can be explained by the fact that this winter we asked the GP's to send in swabs from 1 September onwards while in previous winters we asked to send in swabs from 1 August onwards. This was on request of the NIVEL because of concern about the workload for the GP's: table 3.1 shows that fewer GP's participated this winter compared to recent winters. Furthermore, we asked the GP's to send in a maximum of 1 swab per week during the influenza peak (Appendix II) because of concern of the workload at the laboratory.

The number of nose/throat swabs sent in by the general practitioners was of significance from week 37-40 in 1997 till week 17-20 in 1998 (figure 3.3). The highest number of swabs was received in the period from week 5 (starting 26 January) till 16 (ending 19 April). The number of nose/throat swabs from patients registered with ILI shows the same course (figure 3.4).

Figure 3.2 Distribution over the three degrees of urbanisation in the Netherlands of the 43 general practices (GP) of the Netherlands Institute of Primary Health Care (NIVEL) registering influenza-like illness and of the 30 GP's of the NIVEL taking swabs from patients who consulted them for an acute respiratory infection, winter 1997/98

Table 3.1 Some key characteristics of the NIVEL/RIVM surveillance by winter in the period 1992/93 - 1997/98

	92/93	**93/94**	**94/95**	**95/96**	**96/97**	**97/98**
Culture	yes	yes	yes	yes	yes	yes
PCR	yes	no	yes	no	yes	yes
Bacteriology	no	no	no	no	yes	no
Begin and end week	41-20	39-29	37-25	31-23	30-29	36-27
Number of weeks	32	43	41	45	52	44
Number of participating GP's	35	36	37	31	36	30
Number of swabs	396	293	551	483	541	363
Number of follow-up swabs	0	0	72	0	55	1
Number of positive swabs	126	92	258	171	304	189
% of positive swabs	32%	31%	47%	35%	56%[a]	52%
Range (per GP)	0-75%	0-100%	0-75%	0-100%	0-100%	0-100%
Number of ILI swabs	213	202	344	336	306	251
% of positive ILI swabs	35%	35%	47%	40%	59%	54%
Range (per GP)	0-100%	0-100%	0-100%	0-100%	0-100%	0-100%
% of ILI swabs	54%	69%	62%	70%	57%	69%
Mean number of swabs/GP	11	8	15	16	15	12
Range	1-35	1-25	1-62	2-44	1-69	1-65
Mean number of ILI swabs per GP	6	6	9	11	9	8
Range	0-28	0-18	1-41	2-37	0-28	1-42

a) 64% with bacteriology

The age distribution of the ARI-patients from whom a nose/throat swab was sent in during winters 1992/93-1997/98 and during winter 1997/98 alone is comparable with the age distribution of the Dutch general population (figure 3.5). There is some over-sampling of the youngest age category (0-4 years) and some under-sampling of the oldest age category (> 64 years).

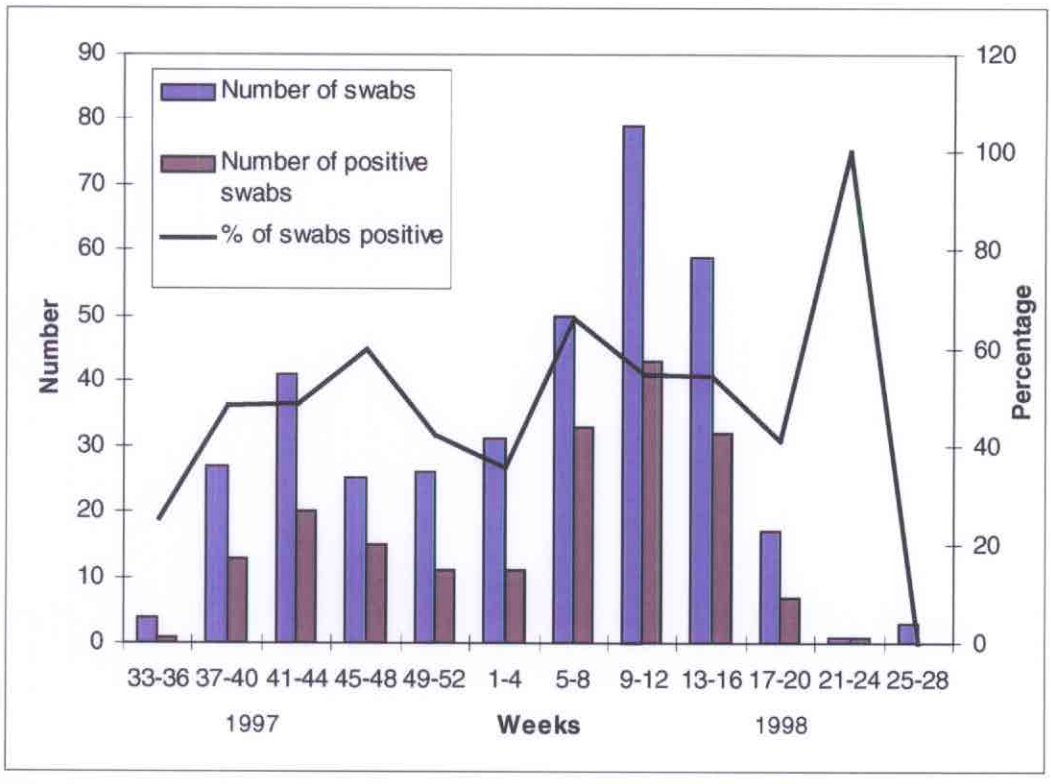

Figure 3.3 Number of (positive) nose/throat swabs from patients with an acute respiratory infection who consulted their general practitioner per 4-week periods during winter 1997/98 in the Netherlands (total n=363). From five swabs herpes simplex virus (HSV) was isolated. In three of these swabs another m.o. was detected, too. Since HSV is not likely to cause respiratory symptoms in immuno-competent people, the two swabs in which only HSV was detected were classified as 'no m.o. detected'. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL)

3.2 Micro-organisms detected

As shown in table 1 and figure 1 of part 2, in all swabs taken together influenza viruses and rhinoviruses were the m.o. detected most often (in 23% en 21% of the swabs respectively). Influenza virus was isolated six times more often in swabs from patients registered with ILI, (31%) than in swabs from patients not registered with ILI (5%).

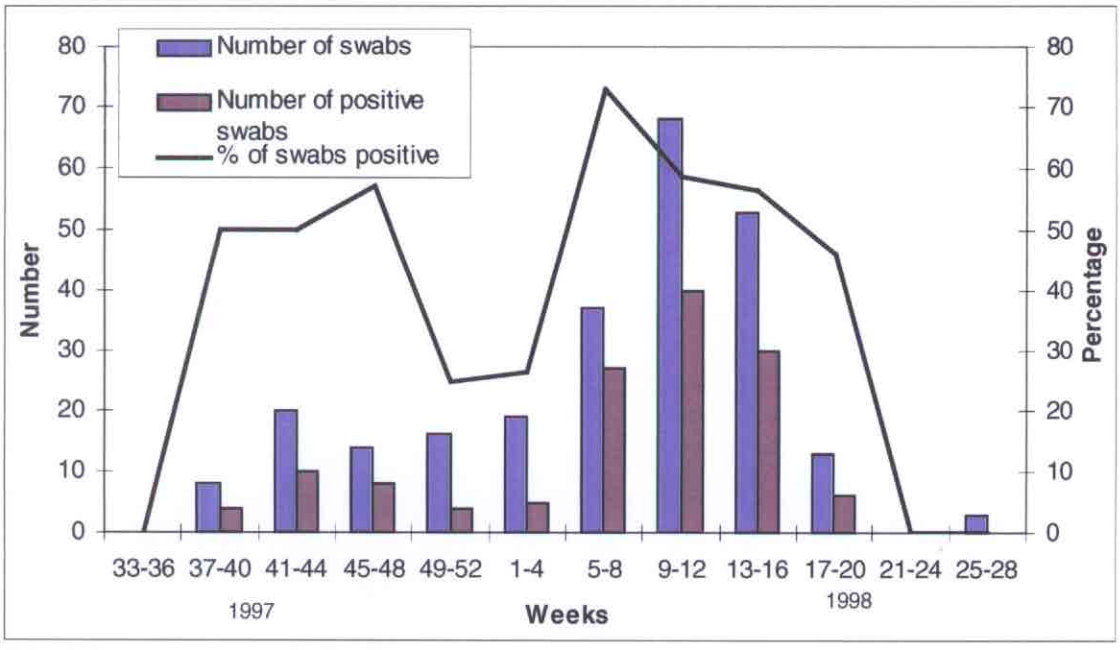

Figure 3.4 *Number of (positive) nose/throat swabs from patients registered with an influenza-like illness who consulted their general practitioner per 4-week periods during winter 1997/98 in the Netherlands (total n=251). From four swabs herpes simplex virus (HSV) was isolated. In three of these swabs another m.o. was detected, too. Since HSV is not likely to cause respiratory symptoms in immunocompetent people, the swab in which only HSV was detected was classified as 'no m.o. detected'. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL).*

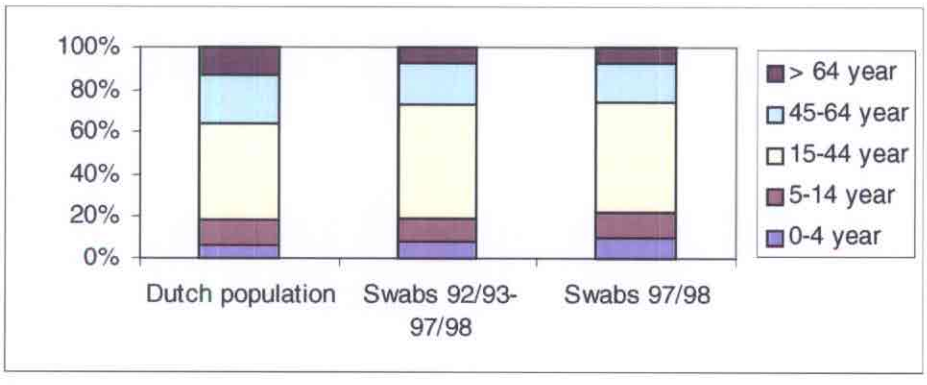

Figure 3.5 *Age distribution of the Dutch general population (at 1-1-1996; Central Bureau for Statistics) and of patients who consulted their general practitioner for an acute respiratory infection of whom a nose/throat swab was taken, NIVEL/RIVM-surveillance, winters 1992/93 - 1997/98*

Table 3.2 Micro-organisms (m.o.) detected in nose/throat swabs from patients registered with an influenza-like-illness who consulted their general practitioner for an acute respiratory infection during winter 1997/98 in the Netherlands (n=251)[a-c]

Micro-organism	Number by culture	Number by PCR	Total number	Total detected as percentage of all submitted swabs	Total detected as percentage of all m.o. detected
Influenza virus	77	ND	77	31	54
Rhinovirus	11	40	40	16	28
M. pneumoniae	ND[d]	9	9	4	6
Enterovirus	2	11	11	4	8
RS-virus	1	3	3	1	2
Adenovirus	2	ND	2	1	1
Parainfluenza virus	0	ND	0	0	0
C. pneumoniae	ND	1	1	0.4	1

a) Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL)
b) From 11 patients with an acute upper respiratory infection the influenza-like illness status was not registered.
c) From four swabs herpes simplex virus (HSV) was isolated. In three of these swabs another m.o. was detected, too. Since HSV is not likely to cause respiratory symptoms in immunocompetent people, the swab in which only HSV was detected were classified as 'no m.o. detected'.
d) Not determined.

Table 3.3 Micro-organisms (m.o.) detected in nose/throat swabs from patients <u>not</u> registered with an influenza-like-illness who consulted their general practitioner for an acute respiratory infection during winter 1997/98 in the Netherlands (n=101)[a-c]

Micro-organism	Number by culture	Number by PCR	Total number	Total detected as percentage of all submitted swabs	Total detected as percentage of all m.o. detected
Influenza virus	5	ND	5	5	9
Rhinovirus	8	32	32	32	60
M. pneumoniae	ND	7	7	7	13
Enterovirus	0	3	3	3	6
RS-virus	0	4	4	4	8
Adenovirus	0	ND	0	0	1
Parainfluenza virus	2	ND	2	2	4
C. pneumoniae	ND	0	0	0	0

a) Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL).
b) From 11 patients with an acute upper respiratory infection the influenza-like illness status was not registered.
c) From one swab herpes simplex virus (HSV) was isolated. Since HSV is not likely to cause respiratory symptoms in immunocompetent people, this swab was classified as 'no m.o. detected'.
d) Not determined.

However, in 23% of the patients registered with ILI, other respiratory pathogens than influenza virus were detected and in 46% no m.o. was detected. Detection of a rhinovirus was twice as likely in swabs from non-ILI patients (32%) than in swabs from ILI-patients (16%) (figure 1 of part 2, table 3.2. and 3.3). A similar picture emerged in previous winters[2, table 25].

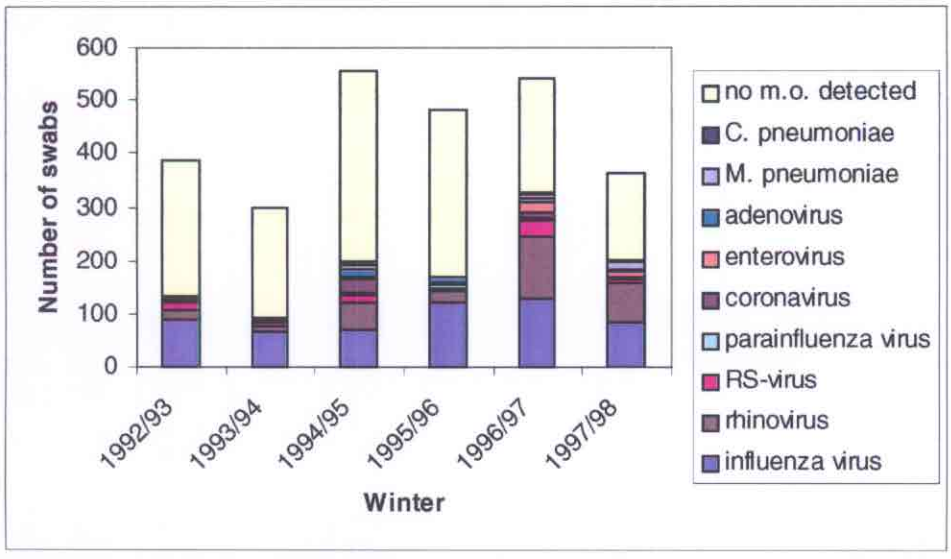

Figure 3.6 Number of nose/throat swabs received from patients who consulted their general practitioner for an acute respiratory infection plus the micro-organisms detected in those swabs, winter 1992/93-1997/98 in the Netherlands. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL)

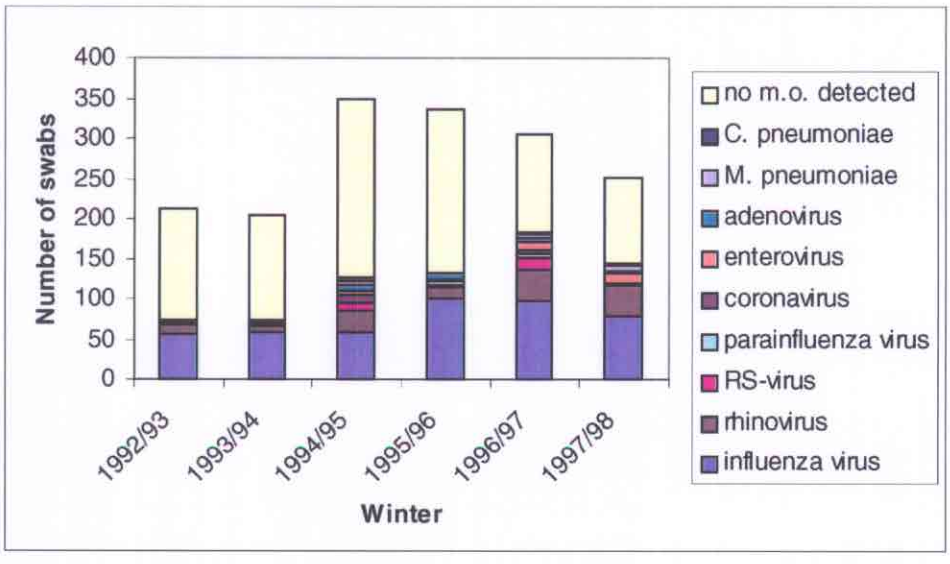

Figure 3.7 Number of nose/throat swabs received from patients who consulted their general practitioner for an influenza-like illness plus the micro-organisms detected in those swabs, winter 1992/93-1997/98 in the Netherlands. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL).

In all swabs taken together and in swabs from patients registered with ILI, approximately 80% of the m.o. detected were influenza viruses and rhinoviruses (table 1 of part 2 and table 3.2). In swabs from patients not registered with ILI, rhinovirus alone accounted for 60% of

the m.o. detected (table 3.3). In preceding winters[2-6] a similar picture of detected m.o. emerged, both for ARI (figure 3.6) and ILI patients (figure 3.7) although the m.o. sought for and the methods used varied over the different winters (table 3.1 and 3.4).

Table 3.4 Micro-organisms sought for and diagnostic methods used in the NIVEL/RIVM surveillance of acute respiratory infections in general practitioners patients by winter in the period 1992/93 - 1997/98

Micro-organism	Method	92/93	93/94	94/95	95/96	96/97	97/98
Influenza virus	Culture	*	*	*	*	*	*
Influenza virus	PCR	*					
Rhinovirus	Culture	*	*	*	*	*	*
Rhinovirus	PCR			*		*	*
RS-virus	Culture	*	*	*	*	*	*
RS-virus	PCR	*		*		*	*
Parainfluenza virus	Culture	*	*	*	*	*	*
Adenovirus	Culture	*	*	*	*	*	*
Enterovirus	Culture	*	*	*	*	*	*
Enterovirus	PCR			*		*	*
Coronavirus	PCR			*		*	
Herpes simplex virus	Culture	*	*	*	*	*	*
C. pneumoniae	PCR			*		*	*
M. pneumoniae	PCR			*		*	*

Rhinoviruses were most prevalent from September until December, whereas influenza viruses prevailed from January till April, both in all swabs (figure 2 of part 2) and in the swabs of the patients registered with ILI (figure 3.8).

Half of the nose/throat swabs from which influenza virus was isolated in winter 1997/98, was obtained from patients 15-44 years old (figure 3.9). This is not surprising, since this age category is the biggest. A similar age distribution of swabs positive for influenza virus was observed over the total period 1992/93-1997/98 (figure 3.10). The age distribution of swabs in which a rhinovirus was detected resembles that of swabs in which an influenza virus was detected; the preponderance of patients between 15-44 years was even bigger. This observation is valid for the period 1992/93-1997/98 and for winter 1997/98 alone. Swabs in which RS-virus was detected were mainly obtained from children 0-4 years old (especially in winter 1997/98), but not exclusively (figure 3.9 and 3.10).

Another way to look at this, is shown in figure 5 of part 2. The percentage of swabs in which a m.o. was detected decreased with age. Influenza virus was detected in about 40% of swabs from patients aged 0-14 years and in about 15% of swabs from patients aged 15 years or over. Rhinovirus was most frequently detected in swabs from patients aged 0-4 and 15-44 years. Hypothetically, this could be explained as follows: elderly react less fierce to ARI than younger people (e.g. they develop fever less quickly), therefore elderly consult their GP later in the process of such an infection (if they consult their GP at all) than younger people. However, our data do not show a relationship between age of the patient and duration of symptoms at the time of swab taking (data not shown).

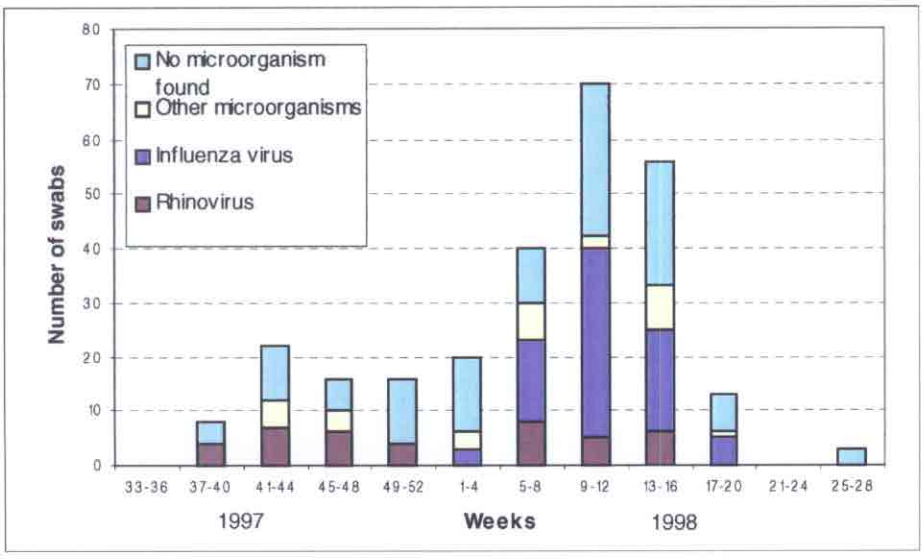

Figure 3.8 *Number of influenza viruses, rhinoviruses and other micro-organisms (m.o.) detected in 251 nose-throat swabs from patients who consulted their general practitioner for influenza-like illness per 4-week periods during winter 1997/98 in the Netherlands. From four swabs herpes simplex virus (HSV) was isolated. In three of these swabs another m.o. was detected, too. Since HSV is not likely to cause respiratory symptoms in immunocompetent people, the swab in which only HSV was detected was classified as 'no m.o. detected'. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL)*

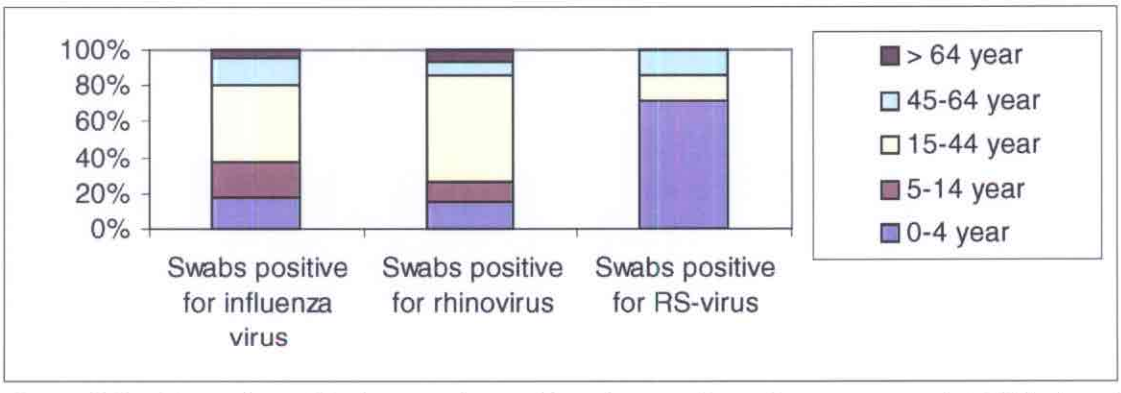

Figure 3.9 *Detection of influenza virus, rhinovirus and respiratory syncytial (RS) virus in nose/throat swabs of patients who consulted their general practitioner for an acute respiratory infection during winter 1997/98. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL)*

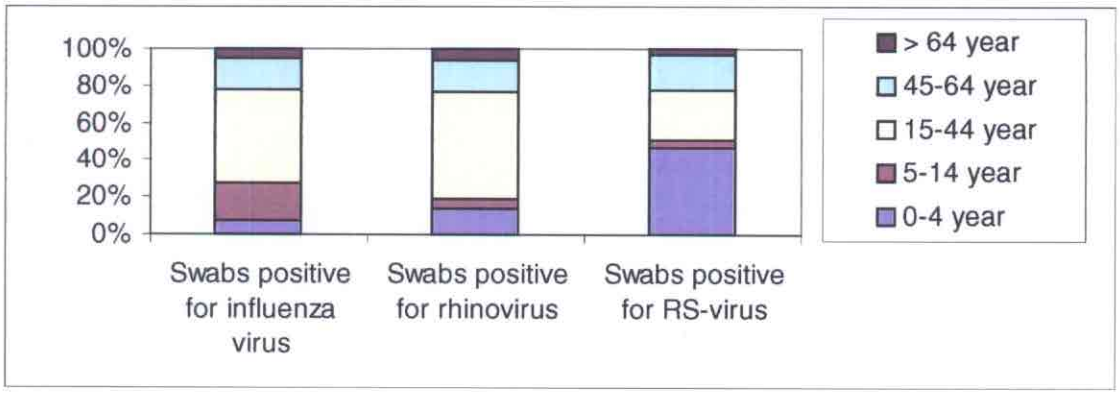

Figure 3.10 Detection of influenza virus, rhinovirus and respiratory syncytial (RS) virus in nose/throat swabs of patients who consulted their general practitioner for an acute respiratory infection during winters 1992/93 - 1997/98. Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL). During winters 1994/95, 1996/97 and 1997/98 the swabs were tested for rhinovirus and RS virus by PCR, too.

3.3 Multiple infections

In the 17 multiple infections found (i.e. 5% of all swabs and 9% of the positive swabs), one of the two m.o. detected was always a rhinovirus, an enterovirus or a herpes simplex virus. In 7 cases, the combination influenza A(H3N2) and rhinovirus was found (table 3.5). The multiple infection cases were 8 men, 8 women and 1 person of unknown sex, varying in age from 4 months to 75 years.

Table 3.5 Combinations of micro-organisms found in multiple infections detected in nose/throat swabs from patients who consulted their general practitioner for an acute respiratory infection during winter 1997/98 in the Netherlands[a]

Micro-organism	Influenza A(H3N2) virus	Rhinovirus	Herpes simplex virus	Total
Rhinovirus	7			7
Enterovirus	3			3
Herpes simplex virus	1	1		2
RSV		2	1	3
Mycoplasma pneumoniae		2		2
Total	11	5	1	17

a) Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL).

In the winters 1994/95[4] and 1996/97[2], seasons in which the same m.o. were analysed by the same methods as in winter 1997/98 plus coronavirus, in 4-6 % of all swabs and in 16% of the positive swabs multiple infections were detected. *Chlamydia* or *Mycoplasma pneumoniae* was found in relatively many multiple infections in winters 1994/95 and 1996/97, but not in winter 1997/98 (table 3.6). In winter 1997/98 60% of the HSV detected was found in multiple infections. The rate of multiple infections was lower in winters 1992/93, 1993/94 and 1995/96 than in winters 1994/95, 1996/97 and 1997/98 described above because PCR analyses were not carried out in the former winters (data not shown).

Table 3.6 Micro-organisms found in multiple infections as percentage of the total amount of times a micro-organism was detected in nose/throat swabs from patients who consulted their general practitioner for an acute respiratory infection during winter 1997/98 in the Netherlands[a]

Micro-organism	Number of times in multiple infection	Total amount of Times detected	Percentage in multiple infection
Rhinovirus	12	76	20
Influenza A(H3N2) virus	11	83	13
Enterovirus	3	14	21
Herpes simplex virus	3	5	60
Mycoplasma pneumoniae	3	16	19
Respiratory syncytial virus	2	7	29

a) Swabs taken by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL).

3.4 ILI and influenza virus infection

As described by Claas *et al.*[1], the influenza season started late and was of moderate seriousness in winter 1997/98 in comparison with previous years[2-6]: only in week 7 of 1998 the number of ILI per 10.000 inhabitants as registered by the NIVEL sentinel general practitioners started to rise (figure 3 of part 2). However, already in week 52 of 1997 the first influenza virus (A(H3N2)) of the winter had been isolated from a one-year-old hospital patient[1]. Subsequently, ILI activity was increased during 8 weeks: from week 8 to 15 ILI activity varied between 11 and 17 per 10.000 inhabitants. Only in week 18 of 1998, ILI activity returned to baseline values (figure 3 of part 2).
The NIVEL GP's took nose/throat swabs from 8% of the ILI patients they registered (table 3.8). The majority of the influenza viruses isolated from these nose/throat swabs of patients with ILI was of the A(H3N2) type (n=72); four influenza B viruses and one influenza A(H1N1) virus were isolated. The same predominance of influenza A(H3N2) virus was seen in influenza viruses isolated from hospital patients: no influenza B virus and three influenza A(H1N1) viruses were isolated from hospital patients[1].
As described in part 2, registration of ILI and isolation of influenza viruses from nose/throat swabs of patients registered with ILI were reasonably consistent with each other (figure 3 of part 2). By combining the two, we estimated the incidence of influenza virus infection in the Dutch population, taking into account that:

a) not all infections with influenza virus will lead to (serious, ILI-like) symptoms,
b) not all people with an influenza virus infection will consult their GP; it is estimated that about 33% of adults ([7,8] plus personal communication from J.J. Kerssens, NIVEL) and 70% of children aged 0-4 years (personal communication from J.J. Kerssens, NIVEL) consult their GP when they suffer from an influenza virus infection,
c) not all people who consult their GP for ILI are infected by the influenza virus (as shown above),
d) we cannot detect influenza virus in all swabs of people who are really infected by influenza virus,
e) GP's from the NIVEL sentinel surveillance network register ILI five days per week,
f) GP's from the NIVEL sentinel surveillance network take swabs from a random selection of their ILI patients on four days per week.

We can adjust our estimate of the incidence of influenza virus infection in the Dutch population for factors b, c and e:

influenza virus infection incidence per 10,000 inhabitants = ILI * 7/5 * b * N_i/N_a

in which

ILI = number of influenza-like illnesses per 10,000 inhabitants registered by GP's from the NIVEL sentinel surveillance network,

7/5 = correction factor for the fact that GP's register ILI 5 days per week,

b = correction factor for the number of patients with ILI who do not consult their GP; 1.4 for children aged 0-4 years and 3 for people more than 4 years old,

N_i = number of swabs from patients who consult their GP for ARI and registered with ILI in which influenza virus was isolated,

N_a = number of swabs from patients who consult their GP for ARI and are registered with ILI,

N_i/N_a = "laboratory-based correction factor".

In winter 1997/98, the overall incidence of ILI as reported by the GP's from the NIVEL sentinel surveillance network was 172 per 10,000 inhabitants registered by these GP's from week 40 in 1997 till week 20 in 1998 (table 3.7). This is lower than in most previous winters. On average over the last six influenza seasons, the incidence of ILI was 230 from week 40 in year *n* till week 20 in year *n+1* per 10,000 inhabitants registered by the NIVEL-GP's (i.e. on average 7 per week per 10,000 inhabitants). In the past twenty years, ILI incidence was 2-4 per 10,000 inhabitants per week outside the influenza epidemics[2]. Although influenza is a disease that strikes people of all ages, the incidence of ILI reported by the NIVEL-GP's differs for the various age groups: in every winter since 1992/93 the highest ILI incidence was reported for children 0-4 years old and the lowest for people over 64 years old (figure 4 in part 2, table 3.7, figure 3.12). In winter 1997/98 the incidence of ILI reported for children 0-4 years old was more than twice the incidence reported for the other age groups (table 3.7, figure 3.11).

Table 3.7 Incidence of influenza-like illness per 10,000 inhabitants from week 40 till week 20 registered by general practitioners from the Netherlands Institute of Primary Health Care (NIVEL) sentinel network, by age category and winter

Age (years)	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
0-4	502	581	261	430	320	381	413
5-14	424	328	143	261	203	164	254
15-44	280	242	197	230	206	151	218
45-64	225	285	183	254	221	167	222
> 64	194	236	122	200	195	172	186
All ages	286	280	182	248	248	172	230

The laboratory-based correction factor was age-dependent, too (table 3.8): the highest value was found for children aged 5-14 years. When the incidence of influenza virus infection in the general population was estimated by the formula above, the highest incidence was found in children 5-14 years old, followed by children 0-4 years old (table 3.9, figure 3.11). Over the six winters studied, estimated incidence of influenza virus infection was more than twice as high in children 5-14 years old than in the other age categories and the estimated incidence of influenza virus infection was relatively low in persons > 64 years.

Table 3.8 Calculation of a laboratory-based correction factor (described on page 25) to calculate the incidence of influenza virus infection, winters 1992/93 - 1997/98, by age group, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Age (years)	Mean patient population NIVEL	Number of ILI reported to NIVEL[a]	Number of swabs from ILI-patients (%)[a,b]	Number of swabs from ILI-patients positive for influenza virus (%)[a,b]	Laboratory-based correction factor
0-4	8,054	1,994	126 (6%)	35 (28%)	0.28
5-14	16,958	2,582	174 (7%)	81 (47%)	0.47
15-44	66,534	8,698	891 (10%)	217 (24%)	0.24
45-64	31,435	4,192	323 (8%)	73 (23%)	0.23
> 64	18,676	2,086	121 (6%)	25 (21%)	0.21
Total	141,657	19,552	1,635 (8%)	431 (26%)	0.26

a) Cumulative over the six winters studied.
b) Age was unknown for one patient registered with ILI.

On average, the estimated incidence of influenza virus infection was 251 per 10,000 inhabitants regardless of age in the last six winters from week 40 in year *n* till week 20 in year *n+1* (table 3.9, figure 3.12).

Table 3.9 Estimated incidence[a] of influenza virus infection per 10,000 inhabitants from week 40 till week 20 in the general population of the Netherlands, by age category and by winter, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Age (years)	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
0-4	275	319	143	236	176	209	227
5-14	837	647	282	515	401	324	501
15-44	282	244	199	232	208	152	220
45-64	217	275	177	245	213	161	214
> 64	171	208	108	176	172	152	164
Total	312	306	199	271	271	188	251

a) The incidences were estimated as described on page 25.

The relatively low estimated incidence of influenza virus infection in elderly may be related to the fact that a high percentage of people over 64 years is vaccinated against influenza in the Netherlands (76% in 1997)[9].
It is striking that the laboratory-based correction factor and the estimated incidence of influenza virus infection are relatively very high in the age group 5-14 years. The laboratory-based correction factor is based on parameters that we measured (see page 25). The number of swabs from ILI patients as percentage of the number of swabs from all ARI patients was not different in the age group 5-14 years compared with other age groups (table 3.8, column 4). However, the percentage of the swabs from ILI patients found positive for influenza virus was almost twice as high in the age group 5-14 years than in the other age groups and therefore the laboratory-based correction factor was almost twice as high, too (table 3.8, column 5 and 6). We have no explanation for this observation. Maybe (parents of) children

aged 5-14 years visit their GP in an earlier phase of an ILI so that the chance of detecting an influenza virus in the swabs from 5-to-14-year-olds is greater than in swabs from older patients. We would expect then that the laboratory-based correction factor for the youngest age group (0-4 years) would be at least as high as in the 5-to-14-year-olds. However, we did not observe this (table 3.8, column 6).

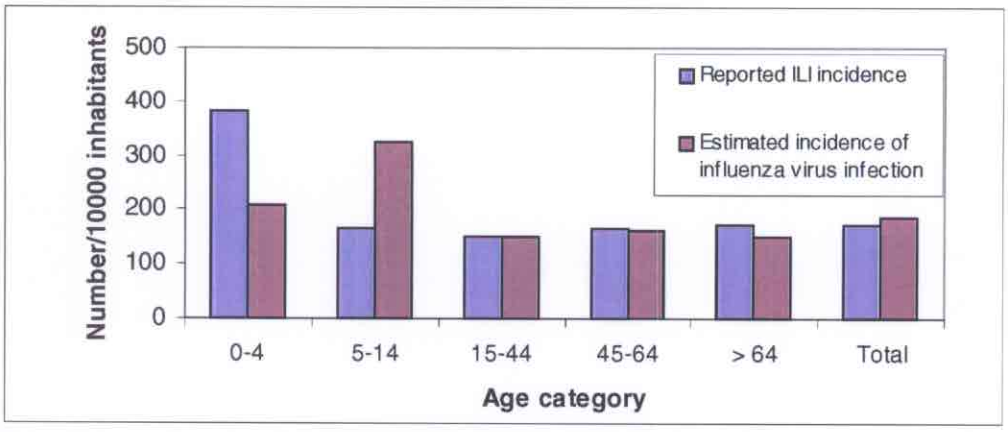

Figure 3.11 Reported incidence of influenza-like illnesses (ILI) and estimated incidence of influenza virus infection from week 40 till week 20 per age category and in total in winter 1997/98 in the Netherlands. Data from the NIVEL/RIVM surveillance of ILI.

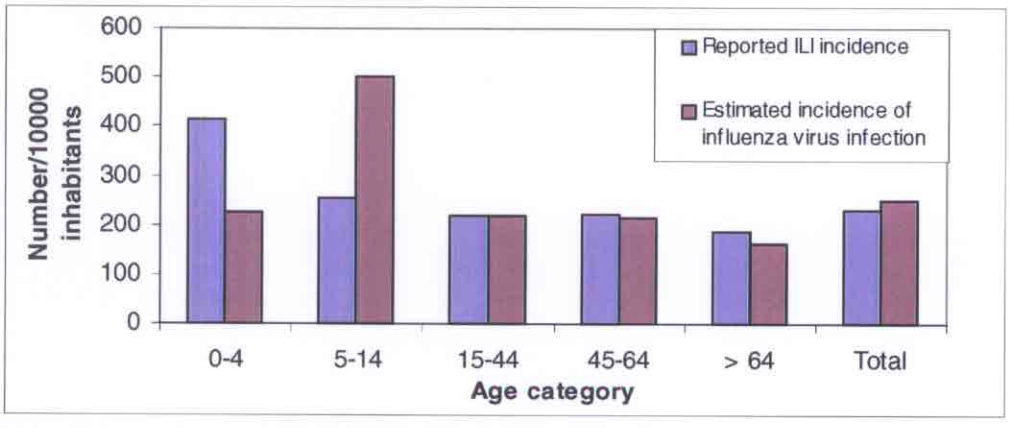

Figure 3.12 Reported incidence of influenza-like illnesses (ILI) and estimated incidence of influenza virus infection from week 40 till week 20 per age category and in total, mean of winters 1992/93-1997/98 in the Netherlands. Data from the NIVEL/RIVM surveillance of ILI.

The estimated incidence of influenza virus infection is not only determined by the laboratory-based correction factor but also by the correction factor for the number of patients with ILI not consulting their GP. Based on literature ([7,8] plus personal communication from J.J. Kerssens, NIVEL) we used 1.4 as value for this correction factor for children aged 0-4 years and 3 for persons 5 years and older. Assuming that 1.4. and 3 are correct values, it is plausible that the value of this correction factor lies closer to 1.4 than to 3 for the children in the lower range of the age category 5-14 years. If we apply 1.4 instead of 3 as value for the

correction factor for GP visits in the age category 5-14 years, the estimated incidence of influenza virus infection becomes 151 per 10,000 inhabitants from week 40 in 1997 till week 20 in 1998. This is in the same range as the estimated incidences for the persons 15 years and older. If we apply 2 as value for the correction factor for GP visits in the age category 5-14 years, the estimated incidence of influenza virus infection becomes 216 per 10,000 inhabitants from week 40 in 1997 till week 20 in 1998. This is in the same range as the estimated incidences for the persons aged 0-4 years. These calculations show that the correction factor for the number of patients with ILI not consulting their GP has a great impact on the estimated incidence of influenza virus infections. Therefore, ideally the values of this correction factor should be validated in a new survey in the Dutch general population (see chapter 4).

Estimating the incidence of influenza virus infection as described here will underestimate the real incidence, even if the corrections made (item b, c and e on page 24) are correct. For instance, there is variation in the time between onset of symptoms and the time of swab taking (1 to 20 days in winter 1997/98, ca. 85% of the swabs were taken $\leq$ 5 days after onset of symptoms as requested (Appendix II); figure 3.13). Further, there is variation in the time the swab is underway from GP to the laboratory (1 to 18 days in winter 1997/98, ca. 65% of the swabs was 1 day underway, ca. 80% 1 or 2 days; figure 3.14). The shorter these time periods, the higher the chance of detecting an influenza virus in the swab if it is there (contributes to item d on page 24) and thus the higher the laboratory-based correction factor will be. If the proportion of people with ILI visiting their GP is smaller than 33% as assumed here, the estimated incidence of influenza virus infection would be higher, too. Of course, there is also a limit to the sensitivity of the detection method used i.e. viral culture (also part of item d on page 24).

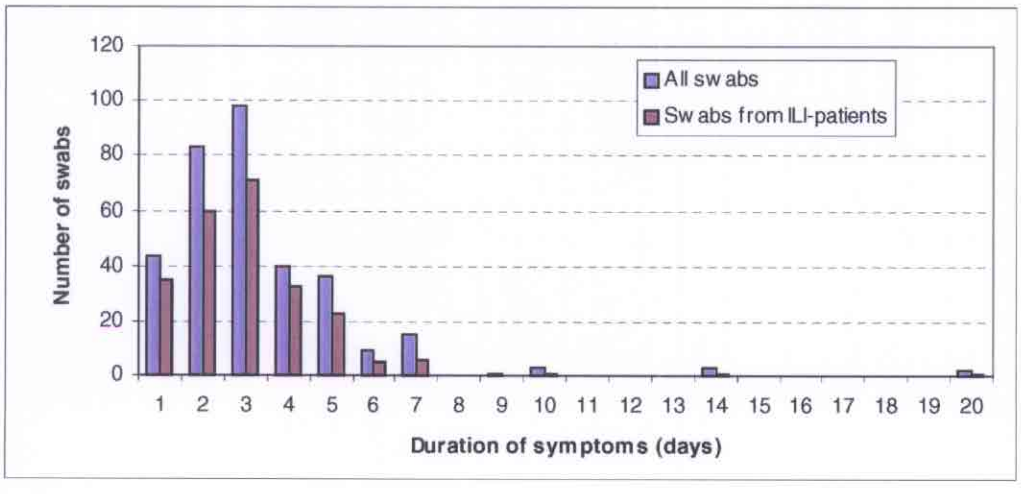

Figure 3.13 Duration of symptoms at the time of taking a nose/throat swab from patients who consulted their general practitioner for an acute respiratory infection, for all swabs and for those from patients registered with influenza-like illness (ILI), NIVEL/RIVM surveillance, winter 1997/98. Duration of symptoms was unknown for 30 swabs, 15 of which were from ILI-patients.

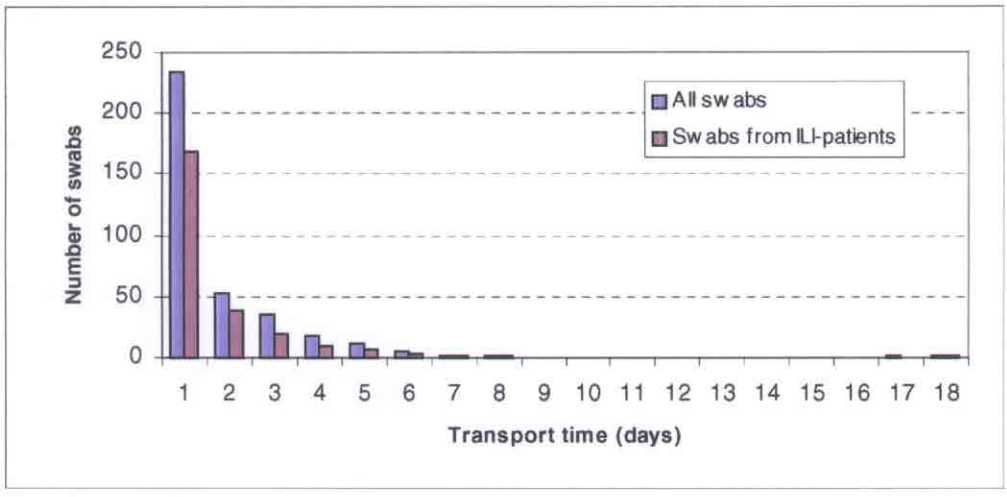

Figure 3.14 Transport time of the nose/throat swabs from general practitioner to the laboratory, for all swabs and for those from patients registered with influenza-like illness (ILI), NIVEL/RIVM surveillance of acute respiratory infections, winter 1997/98

The incidence of influenza virus infection was also estimated by subtype (table 3.10): the highest impact was found for influenza A(H3N2) virus infection in the age category 5-14 year, followed by influenza B virus infection in the age category 5-14 year and influenza A(H3N2) virus infection in the age category 0-4 years. When averaged over all age categories, influenza A(H3N2) virus infection had the greatest impact, followed by influenza B virus infection. The incidence of influenza A(H1N1) virus infection was substantially lower.

Table 3.10 Estimated incidence[a] of influenza virus infection per 10,000 inhabitants from week 40 till week 20 in the Dutch general population, by influenza virus subtype and by age category, average from winters 1992/93 - 1997/98, based on data from the NIVEL/RIVM surveillance of influenza-like illness

Age (years)	A(H3N2)	A(H1N1)	B	Total
0-4	173	26	26	227
5-14	313	18	166	501
15-44	133	7	83	220
45-64	144	6	61	214
> 64	123	0	39	164
Total	163	9	82	251

a) The incidences were estimated as described on page 25.

In a similar fashion the incidence of influenza virus infection by degree of urbanisation was estimated. Reported ILI incidence was highest in villages and lowest in towns in winter 1997/98 (table 3.11). Over the six winters studied, reported ILI incidence was comparable in villages and cities (table 3.11) and higher than in towns. After applying the laboratory-based correction factor (table 3.12), estimated incidence of influenza virus infection was highest in villages and lowest in towns (table 3.13). We expected the incidence of influenza virus infection to be higher in places with a high degree of urbanisation because people live closer

to each other there, so that influenza virus can spread more easily. However, this is not what we observed, in any of the six winters studied. We think this finding is an artefact caused by the higher laboratory-based correction factor for villages than for cities (and towns; table 3.12). The higher laboratory-based correction factor for villages can be explained by the finding that GP's in cities are more likely to take swabs than GP's in villages (table 3.12, column 4) whereas the percentage of swabs found positive for influenza virus is higher in villages than in cities (table 3.12, column 5). Alternatively, the ranking order observed could be real and maybe due to differences in the general condition of people according to degree of urbanisation or in their contacts with other people[2], but we consider this less likely.

Table 3.11 Incidence of influenza-like illness per 10,000 inhabitants from week 40 till week 20 registered by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL), by degree of urbanisation and winter

Urbanisation	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
Village	299	310	236	328	279	264	286
Town	235	240	153	219	184	140	195
City	400	357	226	283	281	227	296

Table 3.12 Calculation of a laboratory-based correction factor to calculate incidence of influenza virus infection (described on page 25), winters 1992/93 - 1997/98, by degree of urbanisation, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Urbanisation	Mean patient population NIVEL	Number of ILI reported to NIVEL[a]	Number of swabs from ILI-patients (%)[a]	Number of swabs from ILI-patients positive for influenza virus (%)[a]	Laboratory-based correction factor
Village	21,110	3,610	141 (4%)	54 (38%)	0.38
Town	90,621	10,477	686 (7%)	161 (23%)	0.23
City	29,905	5,325	818 (15%)	223 (27%)	0.27

a) Cumulative over the six winters studied.

Table 3.13 Estimated incidence[a] of influenza virus infection per 10,000 inhabitants from week 40 till week 20 in the Dutch general population, by degree of urbanisation and by winter, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Urbanisation	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
Village	477	495	377	523	445	421	456
Town	227	232	148	212	178	135	189
City	454	405	256	321	319	257	335

a) The incidences were estimated as described on page 25.

For this NIVEL/RIVM-surveillance the Netherlands is divided in four regions: north (Groningen, Friesland and Drente), east (Overijssel, Flevoland, Gelderland), west (Noord-Holland, Zuid-Holland, Utrecht) and south (Zeeland, Brabant and Limburg). Even though the

Netherlands is a small country, differences in ILI activity between regions are reported (table 3.14). The north reported the lowest ILI activity and the west the highest in winter 1997/98. In previous winters, the north reported the lowest ILI activity too, but mostly the east the highest. The west and the south occupied alternately the second and third rank. After applying the laboratory-based correction factor (table 3.15), the estimated incidence of influenza virus infection was highest in the west (table 3.16), consistent with reported ILI incidence. The estimated incidence of influenza virus infection was lowest in the north and the south. There is no obvious explanation for the observed differences between regions and between winters. As before[2], we could not detect a correlation between the estimated incidence of influenza virus infection by region and by degree of urbanisation.

Table 3.14 Incidence of influenza-like illness per 10,000 inhabitants from week 40 till week 20 registered by general practitioners from the sentinel surveillance network of the Netherlands Institute of Primary Health Care (NIVEL), by region and winter

Region	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
North	201	192	91	176	115	133	151
East	382	363	237	322	259	178	290
West	271	292	151	226	230	204	229
South	295	242	244	265	215	151	235

Table 3.15 Calculation of a laboratory-based correction factor (as described on page 25) to calculate the incidence of influenza virus infection, winters 1992/93 - 1997/98, by region, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Region	Mean patient population NIVEL	Number of ILI reported to NIVEL[a]	Number of swabs from ILI-patients (%)[a]	Number of swabs from ILI-patients positive for influenza virus (%)[a]	Laboratory-based correction factor
North	28,364	2,059	129 (6%)	31 (24%)	0.24
East	31,340	5,353	311 (6%)	94 (30%)	0.30
West	53,490	7,267	783 (11%)	229 (29%)	0.29
South	33,684	4,725	422 (9%)	84 (20%)	0.20

a) Cumulative over the six winters studied.

Table 3.16 Estimated incidence[a] of influenza virus infection per 10,000 inhabitants from week 40 till week 20 in the Dutch general population, by region and by winter, based on data from the NIVEL/RIVM surveillance of influenza-like illness (ILI)

Region	1992/93	1993/94	1994/95	1995/96	1996/97	1997/98	Mean
North	203	194	92	177	116	134	153
East	481	457	299	406	326	224	366
West	330	356	184	275	280	248	279
South	248	203	205	223	181	127	198

a) The incidences were estimated as described on page 25.

4. Concluding remarks and recommendations

As described in previous reports[2-6], acute respiratory infections are very common in the general population. Upper airway complaints are the reason for approximately 25% of the primary visits to general practitioners[10-11]. For effective prevention and control of ARI (including ILI) it is essential to know the relative etiological roles of the various micro-organisms. For example, only in about 30% of the nose/throat swabs from patients registered with ILI (a clinical diagnosis) an influenza virus was detected; in about 23% of the swabs from ILI-patients another micro-organism was detected. This finding can refute unjust claims of influenza vaccine failure. Further, the finding that in more than half of the swabs from ARI patients a virus is detected, supports general practitioners in restrictive prescription of antibiotics for ARI. This is a positive development in view of the growing prevalence of resistance to antibiotics. Another example is that vaccines are being developed against infections with RSV and parainfluenza virus[12]. When these vaccines become available it is essential to know of whom the target groups for vaccination exist. The same holds for the new antivirals that are being developed against infections with e.g. influenza virus (neuraminidase inhibitors)[13-14] and rhinovirus[15]: e.g. the larger the contribution of rhinoviruses to ARI, the more vigorously the efforts will be pursued to develop suitable antiviral substances against these viruses[2].

The NIVEL/RIVM respiratory surveillance is a unique system because it yields information on GP patients (most systems survey hospital patients), because it contains information on ILI incidence since 1970 and information on the aetiology of ARI and ILI since winter 1992/93. Illustrations of the value of surveillance of GP patients next to hospital patients are (a) the finding that RSV infections do not occur exclusively in babies (see page 21-23)[16] and (b) the finding that influenza virus types isolated from GP patients differ from those isolated from hospital patients[2, 17].

The NIVEL/RIVM surveillance is limited to people who develop symptoms after an ARI **and** who consult their GP for these symptoms. To really know what the incidence and seriousness of ARI is in the general population, a population study (analogous tot the current population study with respect to gastroenteritis SENSOR) should be carried out. Before a population study is considered, a case-control study is opportune. The additional value of a case-control study above the current surveillance is that it will give information on which micro-organisms occur in GP patients without respiratory complaints and how often. A case-control study can give information on risk factors for ARI other than the pathogens detected in nose/throat swabs. Furthermore, such a study would give insight in the clinical value of a positive PCR result. Detection by PCR proved to be more sensitive than viral culture for rhinovirus, enterovirus and RSV (part 2). However, information on how long viral RNA can be detected after an infection is still limited[2]. All this information will help to define target groups for prevention and control of acute respiratory infections including ILI.

Currently, the NIVEL GP's are asked to register a patient with ILI if :

- the illness has an acute onset (i.e. a prodromal stage of maximal 3-4 days),
- the rectally measured body temperature is at least 38 °C,
- and if at least one of the following symptoms is present: cough, coryza, sore throat, frontal headache, retrosternal pain, myalgia[18-19].

However, in practice the GP will not check every patient's symptoms with the above criteria. Furthermore, there is a more recent definition of clinical influenza from the Dutch College of General Practitioners[20] (NHG) that differs somewhat from the criteria mentioned above. The NIVEL GP's may well use or at least be influenced by the NHG definition. Govaert *et al.* recommend to use the criteria fever, coughing and an acute onset to register ILI[21]. Most likely, however, the GP will use his/her 'clinical view' and experience to decide to classify a patient with ILI or not. In any case, ILI registration and influenza virus isolation from nose/throat swabs from ILI-patients are reasonably in accordance with each other[2-6 and this report]. If a case-control study would be carried out, it is crucial to have well-defined case and control definitions that are usable in practice.

In the formula we used to estimate the incidence of influenza virus infection by combining reported ILI incidence with the influenza virus detection rate in nose/throat swabs from ILI patients (page 25) we assumed that 33% of patients > 4 years old en 70% of patients 0-4 years old with ILI symptoms in the general population consult their GP for these symptoms. However, these assumptions are based on American data[7], Dutch data from one general practice in winter 1990/91[8] and a Dutch survey from 1994 (personal communication J.J. Kerssens, NIVEL). Ideally, these assumptions would be updated by a new survey in the Dutch general population, especially since we have shown that this correction factor has a great impact on the estimated incidence of influenza virus infection, e.g. in the age group 5-14 years (see section 3.4).

Currently, the NIVEL/RIVM surveillance of ARI (including ILI) consists of ILI registration and ILI swabs plus ARI swabs. Ideally, ARI registration would be added to the surveillance so that estimation of the incidence of the various respiratory micro-organisms can be based on all swabs, not just on those of ILI patients. At the moment we do not know the size of the population the ARI swabs are obtained from such as we know the size of the population the ILI swabs are obtained from, since all ILI patients are registered by the NIVEL GP's.

All NIVEL GP's have received a standard operating procedure on how to take nose/throat swabs. However, as in previous winters, there is variation between the GP's in the number of swabs sent in and the percentage of positive swabs. Since this could have consequences for the representativity of the nose/throat swabs, it would be worthwhile to investigate where exactly these differences originate. As far as practice allows, keeping in mind that surveillance is not the main task of GP's, the procedures should be standardised as much as possible.

In summary:

- this unique surveillance has proven its value and probably will continue to do so in future,
- the current surveillance could be combined with a case-control study,
- the use of the ILI definition by Pel[18-19] may need to be re-evaluated, especially if a case-control study is to be carried out,
- the percentage of the general population with ILI (and preferably also ARI) complaints that consults its GP for these complaints, may need to be re-investigated (by age category, with special attention for the 5-to-14-year-olds),
- it could be considered to register ARI next to ILI,
- the swab taking procedure is to be standardised as much as possible.

Acknowledgements

We thank the general practitioners from the NIVEL sentinel network for registering ILI and taking nose/throat swabs; J.C. de Jong and T.M. Bestebroer for previous reports; M. Heshusius-van Valen (NIVEL) and L.A.M. Werner (RIVM-LIS) for administrative support.

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Appendix I Mailing list

1	Waarnemend Hoofdinspecteur voor de Gezondheidszorg, Drs. P.H. de Vree
2	Hoofdinspecteur voor de Preventieve en Curatieve Gezondheidszorg, Mr. Plokker
3-4	Directeur-generaal van de Volksgezondheid, Prof.dr. H.J. Schneider
5-6	Inspecteur Infectieziekten van de Inspectie Gezondheidszorg, J.K. van Wijngaarden, arts
7-8	Directeur Gezondheidsbeleid, Drs. A.A.W. Kalis
9	Voorzitter van de Gezondheidsraad, Prof.dr. J.J. Sixma
10	Commissie Vaccinatie tegen Influenza van de Gezondheidsraad
11-20	Voorzitter begeleidingscommissie Peilstations NIVEL, Prof.dr. J. van der Zee
21-64	Deelnemende huisartsenpeilstations NIVEL
65-91	Deelnemers European Influenza Surveillance Scheme (EISS)
92	Directeur Nationaal Influenza Centrum, Prof.dr. A.D.M.E. Osterhaus
93	Dr. J.C. de Jong, Erasmus Universiteit Rotterdam, afdeling Virologie
94	Dr. G.F. Rimmelzwaan, Erasmus Universiteit Rotterdam, afdeling Virologie
95	T.M. Bestebroer, Erasmus Universiteit Rotterdam, afdeling Virologie
96	Dr. E.C.J. Claas, Universiteit Leiden
97	Prof.dr. Th.J.M. Verheij, Universiteit Utrecht, vakgroep Huisartsgeneeskunde
98	Prof.dr. H.J. Neijens, Sophia Kinderziekenhuis, Rotterdam
99	Prof.dr. J.L.L. Kimpen, Universitair Medisch Centrum Utrecht
100	Prof.dr. J. Dankert, Amsterdams Medisch Centrum
101	Prof.dr. J. Huisman
102	Landelijke Huisartsen Vereniging
103	Nederlands Huisartsen Genootschap
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135	Hoofd CIE, J. Kool, arts-epidemioloog
136	Plaatsvervangend Hoofd CIE, Dr. M.A.E. Conyn-van Spaendonck
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139	J. Pronk, LIS
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155-175	Bureau Rapportenbeheer
176-200	Reserve-exemplaren

Appendix II Letter of alert to the sentinel general practices of the Netherlands Institute of Primary Health Care (NIVEL) in the beginning of winter 1997/98

NIVEL
nederlands instituut
voor onderzoek van de
gezondheidszorg

drieharingstraat 6
postbus 1568
3500 bn utrecht
telefoon 030 2 729 700
telefax 030 2 729 729

World Health Organization
Collaborating Centre
for Primary Health Care

Aan de Peilstationartsen

datum 26 augustus 1997 kenmerk PEIL 77 AB/MHvV
doorkiesnummer 030-2729 633/634

Geachte collega,

Binnenkort begint het influenza-seizoen weer. Graag wil ik u herinneren aan de afspraken zoals die in voorgaande jaren tot tevredenheid hebben gefunctioneerd.

In het samenwerkingsverband van het NIC (Nationaal Influenza Centrum), het RIVM en de CMR-Peilstations van het NIVEL is het onze taak op elke dinsdag rond het middaguur aan het NIC te melden hoe de 'griep-situatie' in de voorafgaande week was en hoeveel keel-neuswatten in de voorafgaande week zijn ingestuurd en wat, voor zover al bekend, de uitslagen van het laboratoriumonderzoek daarin zijn. Het NIC stelt mede op basis van deze aangeleverde gegevens de Influenza Nieuwsbrief samen en verstuurt de Nieuwsbrief op donderdag naar o.a. de peilstationartsen.

Zonder uw medewerking is de surveillance van influenza-achtige aandoeningen echter ondenkbaar. **Uw aandeel is dat u ons tijdig de weekstaat van de voorafgaande week opstuurt.** Ik wil u vragen indien u over faxapparatuur beschikt van de mogelijkheid gebruik te maken. Dit voorkomt een aantal telefonische verzoeken om opgave van de meest recente griepcijfers.

Naast het registreren van patiënten met een influenza-achtige ziektebeeld en het tijdig verzenden van de weekstaten, wil ik u vragen om vanaf 1 september a.s. **per week bij twee patiënten met een acute viraal aandoende respiratoire infectie,** die u vanwege deze klachten consulteren, een keel- en een neuswat af te nemen en naar het RIVM op te sturen.

-Om er voor te-

Appendix II continued

2
PEIL 77 AB/MHvV

Om er voor te zorgen dat de keuze van de patiënt bij wie u een keel- en een neuswat af gaat nemen volledig willekeurig is, vraag ik u om de monsters af te nemen bij de **tweede patiënt met een acute viraal aandoende respiratoire infectie op dinsdag en bij de tweede patiënt met een acute viraal aandoende respiratoire infectie op woensdag.** Het heeft geen zin om materiaal af te nemen bij patiënten waarbij de ziekte langer dan 5 dagen geleden is begonnen, omdat er dan niet meer voldoende virus aanwezig is. Is dat het geval bij de tweede patiënt op dinsdag of woensdag, dan neemt u een keel- en een neuswat af bij de eerstvolgende patiënt op die dag die aan de criteria voldoet.

Om het aantal monsters enigszins te beperken vragen wij u om in het voorseizoen 2 monsters per week op bovengenoemde wijze af te nemen en om zodra het aantal IAZ dat u turft significant begint toe te nemen, 1 monster per week af te nemen bij de tweede patiënt op dinsdag of op woensdag die daarvoor in aanmerking komt. Wij zullen u hierover een herinneringsbrief sturen als er een griepepidemie is.

Net zoals in voorgaande jaren zal bij het RIVM bepaald worden welke virussen in de keel- en de neuswatten aanwezig zijn. Binnenkort krijgt u het benodigde materiaal (de 'groen verzendzakken') toegestuurd.

Voor vragen over keel- en neuswatten kunt u terecht bij het RIVM bij Klaas Bijlsma of Kees Verwey (tel. 030-274 2392 of 030-274 2247) of bij Marie-Louise Heijnen (project-coördinator, 030-274 2115, maandag t/m donderdag).

Met dank voor uw medewerking,
Hoogachtend,

A.I.M. Bartelds, huisarts-Coördinator CMR-Peilstations

PS.: De dozen met afnamesets voor keel- en neuswatten die in voorgaande jaren zijn gebruikt, zijn vervallen. Ik wil u vragen deze weg te doen. U kunt ze met het normale huisvuil laten afvoeren aangezien er geen schadelijke materialen in verwerkt zijn.

Appendix III Form accompanying nose/throat swabs from patients who consult their general practitioner for an acute respiratory infection in winter 1997/98

VIR-F117

Inzendformulier monsters NIVEL/RIVM virologische surveillance van acute viraal aandoende respiratoire infecties, seizoen 1997/98

Naam arts: .....

Code peilstation: .....

Naam patiënt: .....

Geslacht patiënt: M/V

Geboortedatum patiënt: .....- ..... - 19.....

Ziekteduur: ..... dagen

Datum afname materiaal: .....- ..... - 19.....

□ neuswat □ keelwat

Symptomen:
□ Acuut begin
□ Hoesten
□ Rhinorrhoe
□ Keelpijn
□ Rode keel
□ Dyspnoe
□ Koorts, ...°C
□ Malaise
□ Spierpijn
□ Hoofdpijn
□ Buikpijn
□ Misselijk
□ Braken
□ Diarree

Eventeel de diagnose:
□ Sinusitis
□ Otitis
□ Conjunctivitis
□ Pharyngitis
□ Pseudocroup
□ Tonsillitis
□ Laryngitis
□ Bronchitis
□ Bronchiolitis
□ Pneumonie
□ Tracheïtis

Heeft u de patiënt aangemeld als IAZ?	□ ja	□ nee
Zijn er soortgelijke zieken in de omgeving van de patiënt?	□ ja	□ nee
Heeft de patiënt een influenza-vaccinatie voor dit seizoen?	□ ja	□ nee
Lijdt de patiënt aan een bewezen respiratoire allergie?	□ ja	□ nee
Heeft de patiënt regelmatig contact met kinderen < 5 jaar ?	□ ja	□ nee
Lijdt de patiënt aan immunosuppressie?	□ ja	□ nee
Rookt de patiënt?	□ ja	□ nee
Zo nee, heeft de patiënt ooit gerookt?	□ ja	□ nee

- **Materiaal afnemen tot uiterlijk 5 dagen na het begin van de ziekte, omdat in later afgenomen materiaal te weinig virus aanwezig is.**
- **Materiaal afnemen bij de 2e patiënt met een acute viraal aandoende respiratoire infectie op dinsdag en bij de 2e patiënt met een acute viraal aandoende respiratoire infectie op woensdag.**
- **Materiaal in transportvloeistof direct versturen. Kan dit niet, dan bewaren bij 4 ° C (niet invriezen).**
- **De onbeënte transportvloeistof kan bij kamertemperatuur worden bewaard. De vloeistof blijft op deze wijze 2 jaar bruikbaar.**
- **Als u vragen of opmerkingen heeft kunt u contact opnemen met dhr. Klaas Bijlsma of dhr. Cees Verwey tel. 030-274 2392 of 030-274 2247.**

Niet invullen door inzender
Datum ontvangst materiaal: ..... - ..... - 19.....
Uitslag: ..... Datum: ..... - ..... - 19.....

Appendix IV Poster presented at the European Society of Clinical Virology (ESCV) in Rotterdam, January 1999 and at the Dutch Society for Medical Microbiology (NVMM) in Veldhoven, April 1999

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NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT
Antonie van Leeuwenhoeklaan 9, P.O. Box 1, 3720 BA, BILTHOVEN, The Netherlands, Tel: +31 30 274 91 11, Fax: +31 30 274 29 71

JW Dorigo-Zetsma[1], MLA Heijnen[1], AIM Bartelds[2], B Wilbrink[1] and MJW Sprenger[1]

1 *National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands; E-mail: Wendelien.Dorigo@rivm.nl*
2 *Netherlands Institute of Primary Health Care (NIVEL).*

Surveillance of influenza-like illnesses (ILI) and respiratory pathogens in general practices in The Netherlands in winter 1997/'98

Introduction

The Netherlands Institute of Primary Health Care (NIVEL) is running a surveillance network of 43 sentinel general practice (GP) stations, spread over the country (Fig. 1). The network covers 1% of the Dutch population and represents the total Dutch population with respect to age, sex and degree of urbanisation. The incidence of influenza-like illnesses (ILI) is calculated weekly during the winter season by NIVEL from the data of the network. The system was extended by the RIVM with virus isolation and detection from nose/throat swabs obtained from patients with an acute respiratory infection (ARI), of whom about 70% are registered with ILI.

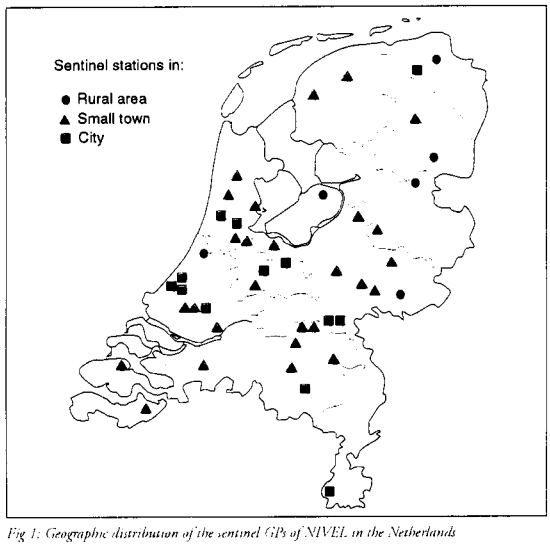

Fig 1: Geographic distribution of the sentinel GPs of NIVEL in the Netherlands

Aim

To provide insight in the etiology of ARI in the general population.

Materials and methods

During winter 1997/'98 general practitioners of 70% of the sentinel practices provided the RIVM with nose/throat swabs from patients with ARI. A total of 364 nose/throat swabs were sent to the RIVM by regular mail and examined by virus isolation and PCR. For virus isolation tMK cells (tertiary cynomolgus monkey kidney cells) and GaBi cells (human diploid fibroblast cells) were used. Identification of viruses was performed using standard procedures. PCR was performed for respiratory syncytial virus (1), rhinovirus and enterovirus (picornaviruses) (2) and *Mycoplasma pneumoniae* (3) and *Chlamydia pneumoniae* (4).

Results

In 52% (189 of 364) of the samples at least one virus or bacterium was detected. (Table) 44% (91 of 206) of the respiratory pathogens were recognised by PCR only. In 5% (17 of 364) of the samples a double-infection was observed. Influenza viruses were detected most often (23% of the samples), followed by rhinoviruses (21% of the samples). (Fig 2) Of the rhinoviruses, 74% was detected by PCR only, whereas 26% was detected by isolation and PCR. Rhinoviruses were most prevalent from September until December, whereas influenza viruses prevailed from January until April.(Fig 3)
Registration of ILI and isolation of influenza viruses were in accordance with each other.(Fig 4) However, in 23% of the patients registered with ILI other respiratory pathogens than influenza virus were detected and in 47% no pathogen was detected.

Conclusions

- Influenza viruses and rhinovirus were the predominant viruses detected in patients with ARI from a GP sentinel system.
- Application of the PCR improved the detection of respiratory pathogens in nose/throat swabs considerably.
- Registration of ILI by GP's was in accordance with isolation of influenza viruses in the laboratory.

Acknowledgements: The authors thank K.Bijlsma, C.Verwey, H. van der Nat and H.Boswijk for excellent technical support.

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Table Pathogens in nose/throat samples from patients visiting their GP with ARI during winter season 1997/'98

Micro-organism (m.o.)	Number	Percentage of total number of submitted samples	Percentage of total number of detected m.o.
Influenza viruses	83	23%	40%
Rhinovirus	76	21%	37%
Mycoplasma pneumoniae	16	4%	8%
Enteroviruses	14	4%	7%
Respiratory syncytial virus	7	2%	3%
Herpes simplex viruses[a]	5	1%	2%
Adenoviruses	2	0.5%	1%
Parainfluenza viruses	2	0.5%	1%
Chlamydia pneumoniae	1	0.3%	0.5%
Total	206	52%[b]	100%

a) In 3 out of 5 samples with a positive culture for Herpes simplex virus (HSV), another pathogen was detected. HSV is not likely to cause respiratory symptoms in immunocompetent people.
b) Counting the individual percentages, the total exceeds 52% because of double-infections.

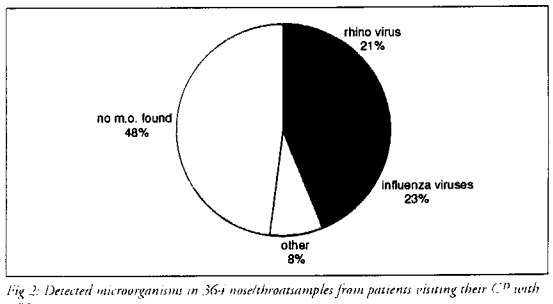

Fig 2: Detected microorganisms in 364 nose/throatsamples from patients visiting their GP with ARI

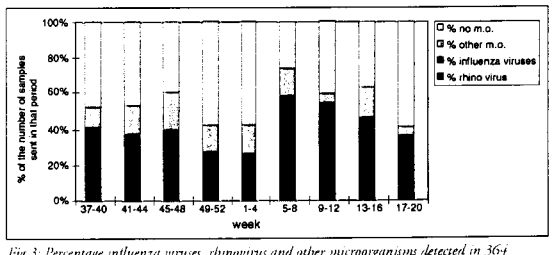

Fig 3: Percentage influenza viruses, rhinovirus and other microorganisms detected in 364 nose/throatsamples from patients visiting their GP with ARI, per 4 weeks in winterseason 97/98

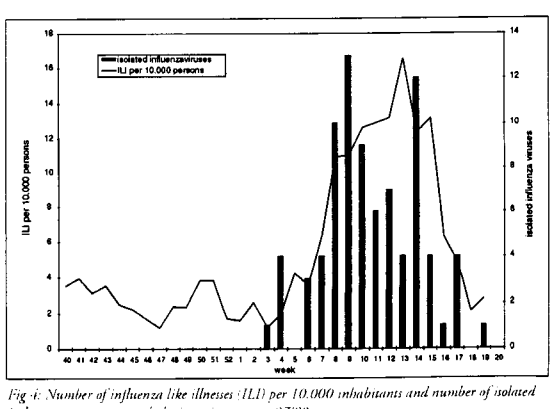

Fig 4: Number of influenza like illnesses (ILI) per 10.000 inhabitants and number of isolated influenza viruses per week during winterseason 97/98

Appendix V Reporting on the NIVEL/RIVM surveillance of acute respiratory infections in winter 1997/98

During the winter, the results of the analysis of the nose/throat swabs are immediately reported back to the GP's that sent in the swabs. The results on ILI activity (NIVEL), influenza virus and RS-virus detection in swabs from GP patients (RIVM) and hospital patients (EUR) are entered in the EISS database by the RIVM. Further, during the influenza season, the ILI registered (NIVEL), the results of the analysis of the nose/throat swabs from GP patients (RIVM) and the results of influenza virus characterisation of Dutch influenza virus isolates (EUR) are reported in the weekly Influenza Newsletter. At the end of the winter, the overall results of the NIVEL/RIVM surveillance are presented in reports as this one[2-6]. The EUR, NIVEL and RIVM report on the Dutch influenza epidemic and the antigenic and molecular characteristics of the influenza viruses isolated that winter in the Netherlands Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde)[1].