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Strengthening the diagnostic capacity to detect Bio Safety Level 3 organisms in unusual respiratory viral outbreaks

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ABSTRACT

Background: Experience with a highly pathogenic avian influenza outbreak in the Netherlands (2003) illustrated that the diagnostic demand for respiratory viruses at different biosafety levels (including BSL3), can increase unexpectedly and dramatically.

Objectives: We describe the measures taken since, aimed at strengthening national laboratory surge capacity and improving preparedness for dealing with diagnostic demand during outbreaks of (emerging) respiratory virus infections, including pandemic influenza virus.

Study design: Academic and peripheral medical-microbiological laboratories collaborated to determine minimal laboratory requirements for the identification of viruses in the early stages of a pandemic or a large outbreak of avian influenza virus. Next, an enhanced collaborative national network of outbreak assistance laboratories (OAL) was set up. An inventory was made of the maximum diagnostic throughput that this network can deliver in a period of intensified demand. For an estimate of the potential magnitude of this surge demand, historical counts were calculated from hospital- and physician-based registries of patients presenting with respiratory symptoms.

Results: Number of respiratory physician-visits ranged from 140,000 to 615,000 per month and hospitalizations ranged from 3000 to 11,500 per month. The established OAL-network provides rapid diagnostic response with agreed quality requirements and a maximum

throughput capacity of 1275 samples/day (38,000 per month), assuming other routine diagnostic work needs to be maintained.

Conclusions: Thus surge demand for diagnostics for hospitalized cases (if not distinguishable from other respiratory illness) could be handled by the OAL network. Assessing etiology of community acquired acute respiratory infection however, may rapidly exceed the capacity of the network. Therefore algorithms are needed for triaging for laboratory diagnostics; currently this is not addressed in pandemic preparedness plans.

1. BACKGROUND

Predicting the course of an emerging infection is challenging as often occurrence, duration, severity, and magnitude cannot be anticipated.[1],[2], [3], [4] and [5] This is illustrated by previously unexpected epidemics like SARS in 2003, highly pathogenic influenza A(H7N7) virus in the Netherlands in 2003 and the currently circulating A(H5N1) virus in Asia[6] and the current threat of emergence of a virus of likely porcine origin. In addition, the ongoing circulation of highly pathogenic avian influenza A(H5N1) virus in birds and the fear that after adaptation this virus could also transmit efficiently between humans, emphasizes the importance of preparing for diseases transmitted by (respiratory or unknown mode or site of infection) viruses. The Netherlands, like many other countries, has developed an integrated plan including triage of patients, diagnostic protocols and communication structures to be used if a new epidemic influenza virus were to arise(http://www.rivm.nl/cib/infectieziekten-AZ/ infectieziekten/Influenza/index.jsp).

This plan rests on several pillars such as protocols for disease control, laboratory diagnostics for patients and contacts, response activities, containment and communication strategies (http://www.rivm.nl/cib/binaries/DB%20Bestrijding%20influenzapandemie%20november%2006 tcm92-33565.doc).

Rapid and sensitive identification of infectious individuals is a cornerstone of control of severe infectious disease outbreaks, and crucial as long as efforts aim at preventing spread of the disease (hence in the early stages of a new pandemic).[7] Several factors tend to increase the diagnostic demand in such an early stage of a new epidemic. Firstly, clinical symptoms due to new influenza virus strains will probably not differ from those caused by other circulating respiratory pathogens. This may limit options for triaging and prioritization of diagnostics through judgment of clinical symptoms only (http://www.cdc.gov/flu/symptoms.htm).[8], [9], [10] and [11] Secondly, the need to trace and test contacts of diagnosed cases can rapidly multiply the number of diagnostic tests needed. Thirdly, measures of containment in dealing with viruses of unknown pathogenicity will put further restrictions on the available laboratory capacity. However, to date, most national preparedness plans do not anticipate for an increase in diagnostic demand in the early stages of an influenza pandemic or for other unexpected respiratory outbreaks. A review of preparedness plans, however, concluded that prioritization of laboratory testing capacity has been addressed poorly in the European countries, unlike several other countries that experienced the SARS and A(H5N1) epidemics.[12] and [13]

Previous experience with a highly pathogenic avian influenza outbreak in the Netherlands (2003) showed that that the diagnostic demand increased and that the coordination of the response to this increase was demanding for the Public Health Laboratory (Center for Infectious Disease Control, RIVM).[5], [14], [15] and [16] Similarly, in Hong Kong, the central public health laboratory experienced a great increase in demand for diagnostics throughout the SARS outbreak (Dr. W. Lim, personal communication). The symptoms were too unspecific to be used in effective triage of patients for the evaluation of SARS.[17] and [18] Also, in Canada, during the SARS outbreak, diagnostics further amplified when case-contacts, i.e. family, nurses, and doctors were assessed to requiring testing. Since SARS assays were not yet implemented in the routine, and specimens required handling at Bio Safety Level 3 (BSL3) http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s6.htm, high numbers of samples were difficult to handle (personal communication, Heinz Feldmann). Circulating human influenza viruses are scaled into BSL2 while highly pathogenic avian influenza, causing serious disease without the availability of a proper treatment, is scaled into BSL3. Since molecular diagnostics on specimens of patients suspected of a BSL3 pathogen can still be performed on BSL2 level, (www.who.org)

regional laboratories performing routine diagnostics are equipped to assist during outbreaks of BSL2 and BSL3 pathogens.

Influenza often is considered to be uncontrollable once it spreads, although the basic reproduction number (R0) (the number of secondary cases a typical single infected case will cause) is estimated at relatively low values of between 1.5 and 3.5 and the basic reproduction number of early stage pandemic influenza may even be lower than that.[19], [20], [21] and [22] However, the serial interval (time between onset of symptoms in an index case and a secondary case) for influenza is very short, and therefore only immediate control measures can potentially stop or mitigate an outbreak in its early phase. It is for such an early stage scenario (the period in which attempts would take place to delay the full force of a pandemic in the Netherlands) that rapid, reliable and specific diagnostics will be needed most. In this scenario an increased diagnostic demand of unknown magnitude, but potentially larger than currently anticipated because of an early public awareness, could arise from any person with respiratory illness as well as from the worried well.[23] Historical numbers of respiratory illness could help to provide a first rough estimate of the potential magnitude of this laboratory demand. These numbers can then be used to guide the laboratory planning of the diagnostic throughput, strategic supplies and allocation of resources required in the early stages of a pandemic.

2. OBJECTIVES

Our aim was to set up a national network of laboratories willing to be involved in preparedness planning, and for handling influenza diagnostics during a pandemic (which we named outbreak assistance laboratories, or OAL). This included agreements on protocols, criteria for declaring a patient positive or negative and the interpretation of these results and quality control criteria. This further included assessing the maximum capacity that could be delivered and how this compared to estimates of required capacity in case of surge demand (based on maximum numbers of patients presenting with respiratory symptoms in historic general practitioner (GP) and hospital data). The members of the OAL jointly identified critical points in preparedness planning. The approach taken provides a useful framework for implementation of influenza or emerging disease preparedness planning for laboratories. To date, the Netherlands has not encountered large viral outbreaks in which an OAL network has been necessary, however, examples like SARS or pandemic influenza demonstrate the potential need of such a laboratory preparedness.

3. STUDY DESIGN

3.1. Selection of partner laboratories

An invitation letter and a questionnaire were sent to all medical laboratories in the Netherlands with a virological diagnostics service. In the invitation letter, the laboratories were asked for their willingness to participate in a virological OAL network for respiratory disease outbreaks. The aim was to set up an active collaborative network of medical-microbiological laboratories with an interest in public health and virology, logistically able and willing to play a role in the diagnostics of viruses (pandemic influenza or other emerging viruses) in the early stages of a pandemic or large outbreak. If yes, they were asked to fill out the questionnaire addressing availability of molecular diagnostics, maximum capacity, biosafety level, and 24-h service ([Table 1]). Meetings were held with representatives from all 9 interested laboratories to set minimal requirements and to agree about the tasks and requirements of the network ([Table 1]).

[TABLE 1.]

Due to the current influenza threat, information on protocols to detect influenza virus A(H5N1), guidelines for sampling and relevant background information were discussed extensively, summarized, and made available at: http://www.rivm.nl/cib/infectieziekten-A-Z/infectieziekten/aviaire influenza/publicatieaviare influenza.jsp.

It was agreed that any updates from the international networks (European Surveillance Influenza Scheme, World Health organization) relevant for preparedness planning would immediately be shared through this website following an e-mail alert.

3.2. Estimating maximum diagnostic demand

  To estimate the diagnostic capacity that would be needed during the early phase of an outbreak with an unknown respiratory pathogen, we analyzed data from different sources to obtain information on the total and peak numbers of patients with respiratory illness in the Netherlands over a number of years. We combined those numbers, where relevant, with estimates for the national coverage rate. Monthly medical registration data for hospitalized patients (with respiratory illness) and for patients seeking care from general practitioners (general respiratory illness and definition of more severe respiratory illness) were analyzed retrospectively (1999–2006 and 2001–2005 respectively) to determine reference values of numbers of patients with respiratory disease in the Netherlands.

3.2.1. General practitioner (GP) diagnoses

  Data was available from the sentinel system of Dutch general practitioners (LINH)[24] which has a coverage of 2% of the Dutch population (approximately 350,000 individuals) and forms a representative sample of the total population regarding age, degree of urbanization, and migrant groups. Symptoms were coded using the International Classification of Primary Care (ICPC) coding system. We used the symptoms registered by these GPs to define two syndromes capturing a general and a more severe lower respiratory tract illness ([Table 2]). The occurrence of pneumonia (which was also included in both definitions of respiratory syndromes) and of fever (not included in either respiratory definition) was assessed separately as well because some symptoms may be more specific or more clinically relevant for a new human influenza virus.

  [TABLE 2].

  For each patient–physician encounter the main three symptoms that were registered per encounter were available. In a sub-analysis we also restricted the respiratory definitions to the use of the 1st registered symptom per encounter only if there was more than one symptom, to distinguish consultations primarily for respiratory disease from those with respiratory disease as complication. Virtually all Dutch citizens are registered with a GP (i.e. family physician), their first point of contact with the Dutch health care system.

3.2.2. Hospital diagnoses

  Hospital discharge diagnoses were obtained from the Dutch National Medical Registry (LMR), with a coverage of all hospitals in the Netherlands (total population = 16.3 million in 2006). Besides the main discharge diagnosis, secondary diagnoses were also available up to a maximum of 10 diagnoses per patient, coded by International Classification of Diseases, Ninth Revision, or ICD9, Dutch variant 1980. A respiratory syndrome was defined as any clinical diagnosis of a respiratory nature with or without a specified causative pathogen with hospitalization data, based on the Centers for Disease Control and Prevention, USA syndrome grouping of ICD9 codes (see [http://www.bt.cdc.gov/surveillance/syndromedef]). We counted the number of such respiratory diagnoses based on both (1) the discharge and any secondary clinical diagnoses and (2) the discharge diagnosis only. The latter was done in case secondary respiratory diagnoses were common respiratory complications of non-respiratory conditions but were not necessarily a reason for the hospitalization.

  [FIGURE 1]

4. RESULTS

4.1. Selection of OAL laboratories and current capacity

  In total, 9 laboratories agreed to serve as outbreak assistance laboratories and eventually to form a national network of outbreak assistance laboratories (OAL) as they satisfied all criteria as specified in [Table 1].

  The 9 OAL laboratories are currently participating in quality control programs for molecular influenza diagnostics (QCMD) and agreed to share these data among all members of the network. They are willing to share protocols and have agreed on the protocols to be used for influenza diagnostics. In the event of a large outbreak, or the onset of a pandemic, the OAL will assist the RIVM with the type and subtype specific diagnostics of the particular virus causing the outbreak. Currently rapid testing for unusual influenza viruses is done at the two laboratories of the national influenza center of the Netherlands: the RIVM and

Erasmus MC with a maximum capacity of approximately 100 and 500 samples a day, respectively, within the routine activities. By setting up and activating the network, the capacity more than doubles and the sites where diagnostics can be performed are evenly spread out geographically, and assuming that all other (routine) diagnostics are continued. Eight of the nine laboratories confirmed to be able to handle 100 samples a day—which was the minimum capacity to be able to join the network. One laboratory confirmed a maximum capacity of 75 samples a day and was still included since it was situated in a region of the Netherlands which was not covered by the other laboratories. Adding up these reported capacities, the estimated maximum detecting and typing capacity for (new) influenza viruses in the Netherlands will be approximately 1275 samples a day (or roughly 38,000 per month). All laboratories have stated that they can continue this intensified diagnostic load for about 3 months. The laboratories rely on the existing route of diagnostic requests submitted by GPs and hospitals, and the already existing logistics of sample transport and exchange. In addition, as long as specimens are from patients suspected (thus not yet proven) of a BSL-3 pathogen infection, molecular diagnostics can still be performed at BSL-2 level, the level at which all routine diagnostics for circulating human influenza viruses is performed.

4.2. Communication structure

The sequences of currently circulating influenza viruses, including avian influenza viruses detected in humans, are checked periodically by the 2 national reference laboratories to identify possible problems with molecular-based detection. When needed, protocols are modified and validated, and the network is informed about adaptations, such as adapted sequences of primers and probes. Recommendations for sample-taking and protocols for diagnostics and typing have been made available to all professionals through the RIVM website (http://www.rivm.nl/cib/binaries/Afnametechniek voor influenza diagnostiek tcm92-35734.pdf# class=). In these documents it is described how sample kits can be ordered, when and how samples from probable cases need to be taken and how the specimen need to be transported to the RIVM. About 8 h after arrival of the specimen, the results of influenza diagnostics are reported to the public health office and GP or medical specialist. It was agreed that at the current levels of testing, the avian influenza and SARS diagnostics will be performed centrally by the RIVM and Erasmus Medical Center in parallel, as recommended by WHO. Implementation of the laboratory preparedness plan will be conducted according to threat assessments (under the responsibility of the Netherlands Center of Infectious Diseases Control which) typically following WHO guidance.

Any changes in level of threat are communicated through a targeted e-mail-based alerting system, which has a "lab-only" alerting option. It was decided that performing rapid diagnostics will be halted when it does not further contribute to knowledge about the course of the disease, or when it does not offer additional information which would be necessary for controlling the epidemic (e.g. when containment efforts are discontinued, and a pandemic is evolving). In that phase, treatment and control measures will be taken on guidance of clinical symptoms only, according to the current national pandemic preparedness plans.

4.3. Estimating background levels of respiratory diagnoses

Depending on the season, the estimated monthly nation-wide prevalence of respiratory hospitalizations varied between 3057 and 11,593 ([Fig. 1]). Restricting analyses to the discharge (or primary) diagnosis only, these numbers were lower (1824 and 8531), albeit less so in the peak of the respiratory season (26% lower) than outside of the season (40% lower). This number of hospitalized cases can be handled with the current outbreak assistance laboratories (for which the maximum capacity was estimated at 38,000 per month).

When taking a broader inclusion, i.e. the incidence of all respiratory illness reported to GPs, the number of cases varied between 860 and 3700 per 100,000 individuals per month, strongly depending on the season. Recalculating these incidences to the total number of individuals in the Netherlands with respiratory complaints shows that the number of patients consulting GPs ranges from 140,000 to 615,000 cases per month ([Table 3], [Fig. 2]). Narrowing this down to the more severe lower respiratory symptoms leads to a much lower estimate of 38,300–162,000 monthly cases (or an incidence of 793–3261 per 100,000, [Fig. 2]). Focusing on only the first diagnosis that was registered by the GP at each consultation, the prevalence of the respiratory syndromes decreased only by approximately 10% ([Table 3]). GP diagnoses of pneumonia show a peak of up to 41,000 cases per month in the respiratory season. Although fever accompanies a wide range of infections, the peak of diagnoses is only approximately half of that of pneumonia, at 23,000 per month ([Fig. 3]). If suddenly a much larger proportion than the usual level of the GP patients (number not known but

currently handled by the Dutch medical laboratories) would suddenly request laboratory testing due to respiratory complaints, the diagnostic capacity of the OAL network is insufficient, given the estimates of persons consulting their GP with respiratory complaints.

[TABLE 3.]

5. DISCUSSION

In conclusion, in the past 2 years a national OAL laboratory network has been set up in the Netherlands to prepare for possible surges in diagnostic demand due to a new pandemic influenza or other unexpected or unusual respiratory disease outbreaks caused by viruses. This network was set up to provide a rapid diagnostic response, with agreed quality requirements, and a known maximum throughput capacity of approximately 1275 samples per day for up to three months, or 38,000 samples per month (of which 600 per day by the National Influenza Center). Our results show that this capacity should be enough to handle a surge in laboratory requests from hospitals, but would probably not be sufficient for a surge in demand arising in the non-hospitalized general community.

[FIGURE 2]

[FIGURE 3]

In principal, each physician can send in samples for diagnostic testing. Although the national guidelines for GPs calls for selective and restricted submission of diagnostic specimens for evaluation, the requests for diagnostics could increase with the threat of a severe disease outbreak. The predicted demand in the general community, based on historic trends, would range from 140,000 to 615,000 cases per month (and probably still an underestimation as not everyone visits their GP with respiratory symptoms) which are numbers that greatly exceed the maximum intensified capacity of the laboratory network (which was estimated at 38,000 per month). In addition, people surrounding a confirmed case, e.g. family or nurses, also need testing, which could increases the number of laboratory test requests dramatically. Narrowing these GP numbers down to more specific lower respiratory complaints presenting to GP's (160,000 cases a month—still too high to be handled by the OAL) may not be desirable, leading to missed cases that can further disseminate disease.[7] Therefore, the most likely scenario would be that other laboratories start testing as well but without the proper preparation which could lead to incorrect diagnoses, given the relatively poor performance in quality control exercises for emerging diseases.[25] and [26]

Therefore, we conclude that a discussion is needed on how the use of diagnostic capacity can be further maximized by triage criteria for diagnostics of community cases of acute respiratory infections in close collaboration with public health officials. If illness in the general community (presenting to GPs) caused by a new pandemic influenza virus cannot be distinguished clinically from other respiratory diseases, the demand for laboratory diagnostics can rapidly increase. This requires a multidisciplinary discussion between virologists, physicians, infection control staff and policy makers on how a potential mismatch between diagnostic demand and laboratory capacity should be handled. Laboratory capacity can be enhanced in the current OAL set-up by minimizing other diagnostics but these will form a competing interest in the hospital-based laboratories.

CONFLICTS OF INTEREST STATEMENT
All authors have declared that no conflicts of interests exist.

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TABLES AND FIGURES

Table 1

Questionnaire topics and minimal laboratory requirements to join a national network of laboratories prepared for large viral disease outbreaks.

Topic	Minimal requirements
Availability for diagnostics	24 h, 7 days a week
Capacity of diagnostics for respiratory viruses	Minimum of 100 samples a day during 2–3 months
Biosafety	Able to unpack samples possibly containing BSl-3 organisms
Presence of routine molecular diagnostics for influenza viruses	Used for routine diagnostics
Turnaround time	8 h
Availability of internal controls in PCR diagnostics	Now used for routine diagnostics
Participation to EQA	Willing to participate in quality control programs and share results

Table 2

Respiratory symptoms and diagnoses reported in general practitioner sentinel data[a].

Respiratory diagnoses by general practitioner included in broad respiratory syndrome	ICPC[b] code	Prevalence 2001–2005 in sentinel data[a]	As proportion of broad respiratory syndrome (%)[c]	As proportion of lower respiratory tract syndrome (%)[c]
Cough	R05	96,008	23	[d]
Acute upper respiratory tract infection	R74	75,617	18	[d]
Acute bronchitis/bronchiolitis	R78	62,005	15	59
Chest symptoms/complaints	L04	36,147	9	[d]
Otitis media acuta/myringitis	H71	29,213	7	[d]
Acute/chronic sinusitis	R75	30,397	7	[d]
Dyspnoe/resp. distress	R02	21,234	5	20
Pneumonia	R81	20,463	5	20
Acute tonsillitis/peritonsillar abcess	R76	14,736	4	[d]
Sneezing, congestion, runny nose	R07	7657	2	[d]
Wheeze	R03	2604	1	[d]
Acute laryngitis/tracheitis	R77	5535	1	[d]
Other respiratory tract infection	R83	2182	1	[d]

[a] Coverage 2% of total Dutch population.
[b] ICPC: International Classification of Primary Care.
[c] Columns do not add up to 100% due to rounding.
[d] Symptom not included in definition of *lower respiratory syndrome*.

Fig. 1. Monthly prevalence of hospitalizations for respiratory illness in the Netherlands, 1999–2006. (Based on Dutch National Medical Registry (LMR), covering all hospitals in the Netherlands. Black line: based on both main discharge and secondary diagnoses. Dashed line: based on main discharge diagnosis only.)
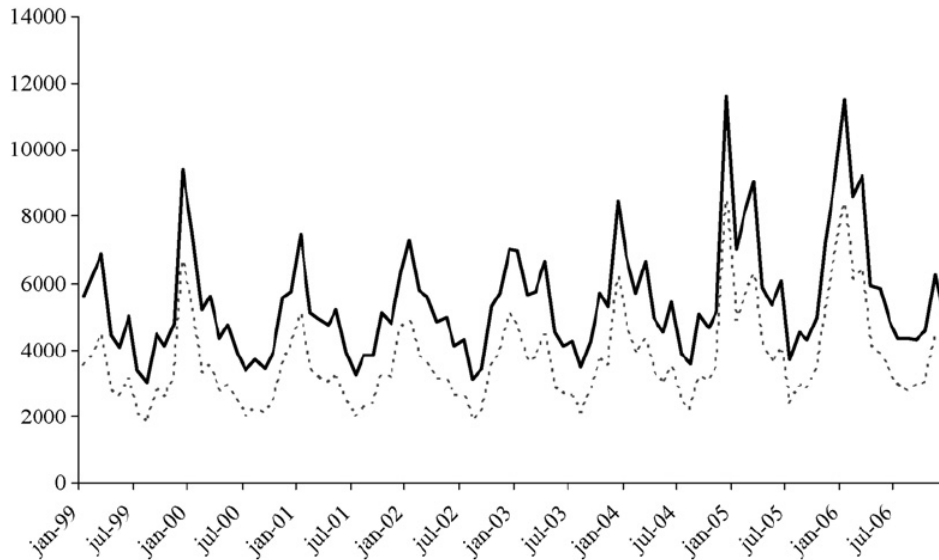

Table 3
Peak monthly prevalence of respiratory diagnoses by GPs in 2001–2005 estimated for total Dutch population[a].

	Maximum monthly prevalence	
	Based on all diagnoses per consultation	Based on the first diagnosis registered on a given consultation (number and as % of first column)
Respiratory diagnoses: broad selection[b]	615,309	556,223 (90%)
Lower respiratory tract diagnoses[b]	162,692	144,833 (89%)
Pneumonia	41,020	
Fever	23,006	

[a] Based on the total number of sentinel visits (coverage 2%), adjusted to the size of the total population of the Netherlands.
[b] See Table 2 for diagnoses (ICPC codes) selected for each respiratory group.

Fig. 2. Monthly prevalence of general respiratory complaints presenting to GPs in 2001–2005. (Based on sentinel system of GPs with a 2% coverage recalculated to numbers
for the total population. Black lines: broad respiratory syndrome. Grey lines: lower respiratory tract diagnoses. Undashed lines: based on any complaint presented per
consultation. Dashed lines: restricted to one (the first) complaint per consultation.)
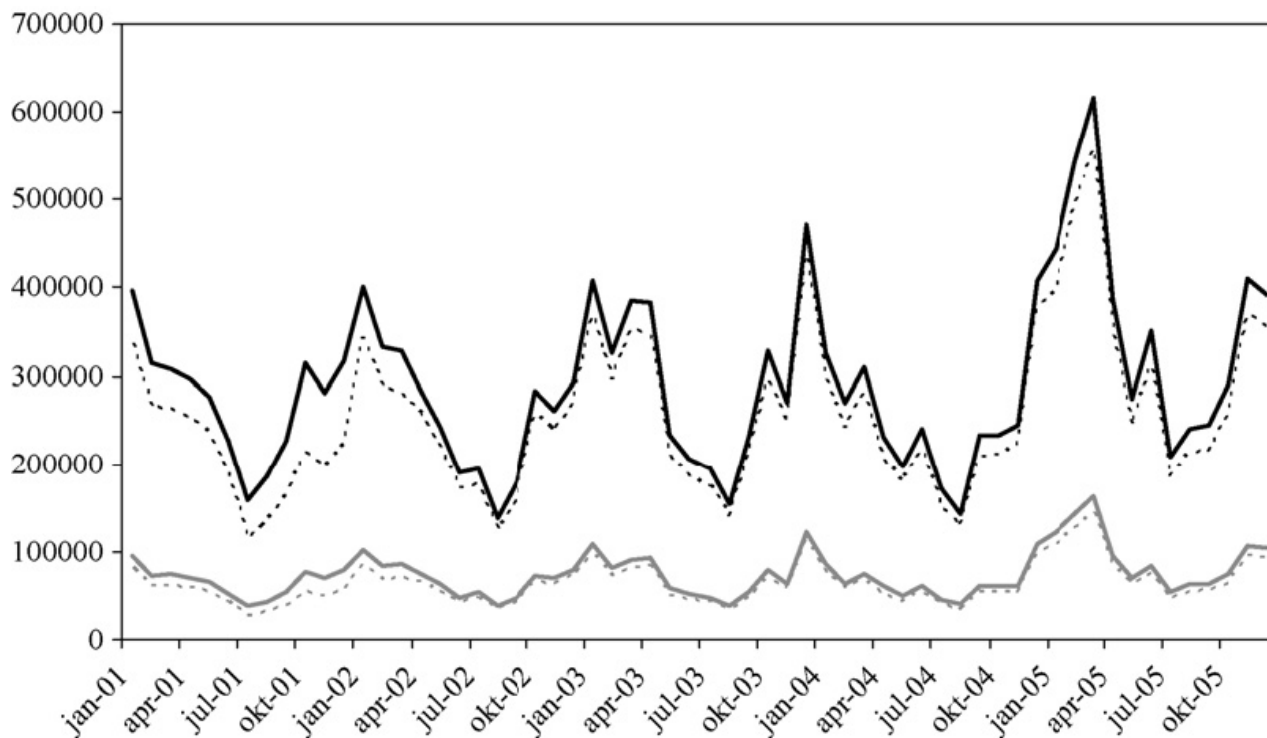

Fig. 3. Monthly prevalence of pneumonia (black line) and fever (grey line) presenting to GPs in 2001–2005. (Based on sentinel system of GPs with a 2% coverage recalculated
to numbers for the total population. black line: pneumonia. Grey line: fever.)