National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Chronological overview of the 2009/2010 H1N1 influenza pandemic and the response of the Centre for Infectious Disease Control RIVM

RIVM Report 215011006/2011

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Colophon

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This research was conducted as commissioned by the Ministry of Health, Welfare and Sport (VWS) within the framework of the project 'Evaluating the policy approach to the 2009 H1N1 pandemic'.

Abstract

Chronological overview of the 2009 H1N1 pandemic and the response of the Centre for Infectious Disease Control RIVM.

The outbreak of the 2009/2010 H1N1 pandemic was a unique test case for infectious disease control in the Netherlands. During the pandemic numerous control measures were implemented at both national and international levels. Events unfolded in rapid succession and were mostly complex in nature, due not only to the actual transmission of the virus in the Netherlands but also to the reactions and responses of international authorities, findings of scientists and the reactions of the public at large.

In the Netherlands, the Minister of Health, Welfare and Sport (VWS) bore the responsibility of coordinating the national response to the influenza pandemic. The Centre for Infectious Disease Control (CIb) of the National Institute for Public Health and the Environment (RIVM), under the authority of VWS, worked in close collaboration with a large number of organizations. The actions undertaken by the CIb went well beyond its routine activities. Under tremendous time pressure, crisis response guidelines needed to be developed and existing ones modified to meet the demands of the situation – all with great care and in close consultation with all parties involved. The many response activities had to be continuously adapted to the changing circumstances.

It is now time to review and evaluate the response. The aim of this report is to provide a systematically documented chronological overview of the many events that took place and the control measures taken during the 2009 H1N1 pandemic from the viewpoint of the CIb. It has been written for policy-makers and health care professionals who were actively involved in the control and the effects of this pandemic. This report was commissioned by the Ministry of Health, Welfare and Sport and is intended to serve – alongside other sources – as core information for the evaluation of the policy adopted in the Netherlands during the 2009 H1N1 pandemic.

Key words:
chronological overview, 2009 H1N1 pandemic, novel influenza A (H1N1) 2009, Mexican flu, influenza, flu, pandemic, infectious disease control

Rapport in het kort

Chronologisch overzicht van de Nieuwe Influenza A (H1N1) 2009/2010 pandemie en de reactie van het Centrum Infectieziektebestrijding RIVM

De Nieuwe Influenza A (H1N1) 2009/2010 pandemie vormde een unieke testcase voor de infectieziektebestrijding in Nederland. Tijdens de pandemie werden er op nationaal en internationaal niveau veel maatregelen getroffen. Gebeurtenissen volgden elkaar snel op en waren complex van karakter, want behalve de virustransmissie in Nederland waren er ook de reacties van internationale instanties, de bevindingen van wetenschappers en de publieke reactie.

In Nederland was de coordinatie van de bestrijding in handen van de minister van Volksgezondheid, Welzijn en Sport (VWS), onder wiens verantwoordelijkheid het Centrum Infectieziektebestrijding (CIb) van het RIVM samen met een groot aantal organisaties nauw samenwerkte. De reactie van het Centrum Infectieziektebestrijding was allerminst routinematig, er moest onder grote tijdsdruk maar wel zorgvuldig en in overleg met betrokkenen crisisrichtlijnen gemaakt en aangepast worden. De vele activiteiten moesten steeds aangepast worden aan de veranderende omstandigheden.

De tijd van terugblikken en evalueren is aangebroken. Doel van dit rapport is om de vele gebeurtenissen en maatregelen rond de Nieuwe Influenza A (H1N1)-pandemie vanuit het oogpunt van het Centrum Infectieziektebestrijding op een overzichtelijke wijze chronologisch in kaart te brengen. Het is geschreven voor beleidsmakers en professionals die betrokken waren bij de bestrijding van (de gevolgen van) deze pandemie. Dit rapport werd opgesteld in opdracht van het ministerie van Volksgezondheid, Welzijn en Sport om – naast andere bronnen – als basisinformatie te dienen voor een evaluatie van het beleid rondom de Nieuwe Influenza A (H1N1)-pandemie.

Trefwoorden:
chronologisch overzicht, Nieuwe Influenza A (H1N1), Mexicaanse griep, varkensgriep, griep, influenza, pandemie, infectieziektebestrijding

Preface

This is the chronological overview of the events and activities that took place during the 2009 H1N1 influenza pandemic that has been drawn up by the Centre for Infectious Disease Control (CIb) of the Dutch National Institute for Public Health and the Environment (RIVM). This chronological overview was written within the framework of the project 'Evaluating the policy approach to the 2009 H1N1 pandemic'; it was commissioned by the Ministry of Health, Welfare and Sport (VWS). This report is a factual account of the pandemic events and activities in which the CIb was actively involved. Very many people have been involved in the realization of this RIVM report. In particular, we would like to thank the following people for their contributions either as reader, reviser or provider of information.

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A great number of different parties were involved in the pandemic, both in the Netherlands and abroad and many preventive and control measures were taken. We would like to thank all those people who were involved before, during and after the 2009/2010 H1N1 pandemic for their efforts.

Contents

1 Introduction

1.1 Background

The Centre for Infectious Disease Control (CIb) was set up to coordinate – at national level and wherever necessary – the prevention and control of outbreaks of infectious diseases. These outbreaks usually occur at local, regional or supraregional level and hardly ever on a national or international scale. The situation that occurred in 2009 was unusual in this respect: within a few months, the Netherlands was having to deal with the consequences of the worldwide pandemic spread of the H1N1 influenza virus. This virus was totally new and, as such, had never spread in humans before. Because it was presumed that hardly anybody would have effective resistance to this new virus, provisions had to be made for the eventuality of large numbers of people becoming ill with some of these people possibly even dying from the infection. On June 11, 2009, the World Health Organization (WHO) declared that the outbreak had turned into a pandemic. At the onset of the pandemic, the WHO estimated that one in three people worldwide would become ill, with the possibility of some of them becoming seriously ill. Luckily, the flu itself turned out to be relatively mild with symptoms similar to the yearly bouts of seasonal influenza. During the 2009 H1N1 pandemic, many response measures were taken at both national and international levels. Initially, these measures were necessary to get to the bottom of the epidemiology and identify the virus characteristics so that the spread from human to human could be prevented as far as possible. Later on, when it became apparent that containment of the outbreak was no longer feasible, the focus changed to one of mitigating the outbreak – in other words, limiting the consequences of infection. In the Netherlands, the Minister of Health, Welfare and Sport (VWS) bore the responsibility of coordinating the national response to the influenza pandemic. The CIb of the Dutch National Institute for Public Health and the Environment (RIVM), under the authority of the Ministry of Health, Welfare and Sport worked in close collaboration with a large number of organizations to tackle the issues surrounding the 2009 H1N1pandemic virus. Unfortunately, the outbreak came at the same time as the epidemic of Q fever in the Netherlands and the commotion surrounding the human papilloma virus (HPV) vaccination. For many people this was a challenging period that only came to an end in July 2010. On August 10, 2010, 14 months after the official onset of the pandemic, the WHO made the official announcement that the 2009 H1N1 pandemic was over.

1.2 Aim

The outbreak of the 2009 H1N1 pandemic was a unique test case for infectious disease control in the Netherlands and in particular for the CIb of the RIVM. It is now time to look back and evaluate the pandemic response in the Netherlands. Now, at the end of 2010, the Minister of VWS has requested an external evaluation report to be drawn up. The core aim of an evaluation should be to provide a good overview of the events that took place. This report aims at presenting nothing more or less than an overview from the perspective of the CIb. For this reason, it is not judgemental but strictly a summary of the events with which the CIb was confronted and how it responded to these events. Events unfolded in rapid succession and were mostly complex in nature; there was not only the transmission and control of the virus in the Netherlands to be considered, but also the reactions from international authorities (WHO, European Centre for Disease Prevention and Control (ECDC), the general public and the findings of scientists. The actions taken by the CIb went well beyond its routine activities. Under tremendous time pressure, crisis response guidelines needed to be developed and existing ones modified to meet the demands of the

situation – all with great care and in close consultation with all parties involved. The diagnostics for this new disease had to be set up and organized for the whole of the Netherlands and the many questions from the public at large and from health care professionals had to be answered. In addition, a massive vaccination campaign had to be organized. These and many other activities had to be continually adapted to the changing pandemic conditions.

The aim of this report is to provide a systematically documented chronological overview of the many events and measures taken during the 2009 H1N1 pandemic from the viewpoint of the CIb. It has been written for all policy-makers and professionals who were involved in any way whatsoever with controlling the effects of this pandemic. Because of the intended readership, detailed explanations of specialist terms will not always be given. This report was commissioned by the Ministry of VWS and is intended to serve – alongside other sources – as core information for the evaluation of the response to the 2009 H1N1 pandemic. This report is a literal translation of the original Dutch report.

1.3 Methodology

It is not possible to describe here every single pandemic event and activity, and for this reason a selection has been made of the events that were significant for the CIb at the time; the actions described here are limited to those in which the CIb played a role. In this respect, this report is not a historical account of the pandemic but a preliminary inventory and arrangement of the events and activities during this period.

It is based on documents in the public domain (WHO, ECDC, RIVM, VWS, Health Council of the Netherlands (GR), and articles from national and international journals) as well as internal reports of CIb meetings, messages conveyed through Inf@ct, the Outbreak Management Team (OMT) and the Administrative Consultative Committee on Infectious Diseases (BAO). Full details of documents frequently referred to can be found in the reference list (A to J). References in the text will be marked with the relevant letter and the date of the specific document. Other documents (e.g. articles, accounts and reports) will be referred to by numbers. Articles on the 2009 H1N1 pandemic are also referred to, but represent only a small proportion of the entire scope of CIb publications on the 2009 H1N1 pandemic, a full list of which can be found in section 9.2. As well as these written documents, we also used information given to us by a group of people who were directly involved in the pandemic response in the Netherlands; we refer to these people as ‘readers’, please see preface.

The account of the facts is documented chronologically. In order to structure the information, the pandemic has been split up into six periods that each focussed on a different aspect of the response; please see section 1.4 for further details. For each of these six periods, the information has been grouped around the following themes: situation, diagnostics, control, government communications, meetings, and vaccination policy. Both the national and international aspects of each of these themes will be described.

1.4 Outline

This report describes what took place during the pandemic period from mid-March 2009 (the point at which the first signals of an outbreak in Mexico were given by the WHO) up to the beginning of August 2010 when the same WHO declared that the pandemic was officially over. The following graph shows the progress of the epidemic in the Netherlands during this period. The information has been taken from the

monitoring stations set up by the Netherlands Institute for Health Services Research (NIVEL).

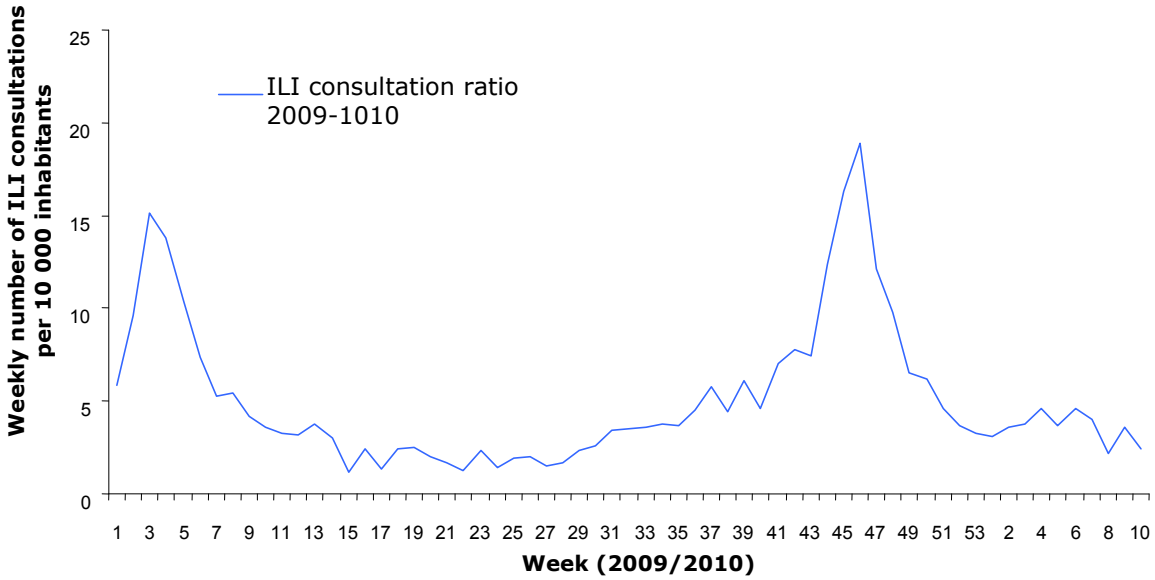

Figure 1 Weekly number of consultations for influenza-like illness per 10,000 inhabitants in 2009/2010. Source: NIVEL monitoring stations.

The report starts (chapter 2) with a description of the most important actors involved in the response. Following this, six separate periods of the pandemic are described (chapters 3-8) which all open with a clear-cut timeline which places the events and activities at national and international level in chronological order.

The six periods are all characterized by a specific event and corresponding activities:

1. The first period (March 18, 2009 - April 29, 2009) starts with the announcement by the health authorities in Mexico. This concerns the outbreak in Mexico and the spread of the disease from Mexico to other places. At this point, the pandemic is still very much a 'foreign' one because the virus has not yet been confirmed in any person in the Netherlands.
2. The second period (April 30, 2009 - June 8, 2009) starts with the first patient being diagnosed in the Netherlands. At this point, there is no question of any spread of the disease in the Netherlands.
3. This situation changes in the third period (June 9, 2009 - June 23, 2009) when there is a limited spread of the disease in the Netherlands.
4. The fourth period (June 24, 2009 - August 15, 2009) is characterized by a change in the prevention and control policy. Preventing the spread of the virus is no longer an objective and the policy becomes one of containing the spread through pandemic influenza mitigation.
5. The next period (August 16, 2009 - November 10, 2009) is the period in which the virus spreads on a large scale; it is also the period in which the vaccination campaign begins.
6. The sixth and final period (November 11, 2009 - August 10, 2010) marks the end of the pandemic with a sharp decrease in the number of cases of 2009 H1N1 flu in the Netherlands and a final announcement by the WHO that the pandemic has ended.

Section 9.1 provides an overview of the research surrounding the 2009 H1N1 outbreak, research to which the CIb is still contributing. Section 9.2 lists the CIb publications on the 2009 H1N1 pandemic and other studies in which CIb employees participated.

2 Actors involved

A large number of organizations were involved in the control of the 2009 H1N1 pandemic in the Netherlands and abroad.

2.1 General practitioners

Infectious diseases fall under a disease category that is commonly seen in general practice. To deal with this category of disease, the general practitioner (GP) carries out the following tasks:

- preventive function: administration of vaccinations, such as the influenza vaccine, and providing information;
- warning function regarding the occurrence of infectious diseases: for example, such diseases as influenza et cetera that could turn into an epidemic;
- requesting diagnostic tests;
- effective treatment of infectious diseases, including the provision of information on self-care, the natural course of the disease and the prevention of complications;
- a gatekeeper function: referring infectious diseases that require specialist treatment due to abnormal disease progression, complications and suchlike.

In accordance with the Public Health Act, GPs are obliged to report certain infectious diseases to the Public Health Services if diagnosis is confirmed or even suspected. This basically means that GPs are the first link in the chain of clinical and microbiological diagnostics prior to notification based on their insight and the information available to them.

Dutch College of General Practitioners
The Dutch College of General Practitioners (NHG) is the professional association for general practitioners in the Netherlands. This association is focussed on promoting scientifically responsible GP work. This is done mainly by making the knowledge obtained from research applicable to general practice, for example, by drawing up standards, guidelines, and patient information such as the ones in place for influenza and vaccination against influenza. An NHG standard was created for an influenza pandemic and accompanied by articles that had appeared in journals including the *Netherlands Journal of Medicine*. The NHG participates in the editorial committee for the digital guideline of the National Influenza Prevention Programme and is a member of the relevant affiliated digital guideline focus group.

National Association of General Practitioners
The National Association of General Practitioners (LHV) represents nearly 11,000 general practitioners in the Netherlands.

2.2 Hospitals/medical specialists

One of the tasks of hospitals and medical specialists is the treatment and diagnostic testing of patients who have been referred to hospital with a probable infection. In addition, they have other duties relating to the management of infectious diseases especially the prevention and control of hospital infections – infections that patients contract during their stay in hospital. Controlling infection is the task of a hospital's medical staff. With a view to preventing hospital acquired infections, hospitals have an Infection Control Committee. Such a committee is a precondition for hospital accreditation. The tasks of the Infection Control Committee are as follows: to determine the frequency and the methods minimally required for surveillance, to

ensure that hospital policy for dealing with the prevention of hospital acquired infections is documented in written protocols, and to draw up protocols for dealing with an epidemic. The people specifically tasked with dealing with infection prevention are the hygienist and the clinical microbiologist. The number of these specialists a hospital has on its staff depends on its size; while a small hospital may have people in part-time jobs only, a large hospital may have a number of people in these positions.

2.3 The Public Health Services

Under the Constitution of the Kingdom of the Netherlands, the government is responsible for taking measures to protect public health. The government has partly transferred this responsibility to the municipal authorities. The Public Health Act states that municipalities must be supported in this task by the Public Health Services (GGD). The implementation and execution of control measures is the task of the departments for infectious disease control at the regional GGDs. The Netherlands as a whole is covered by 28 regional GGDs. Legislation dictates that doctors must report certain specified infectious diseases to the GGD. It is then the task of the GGD to detect the source of the infection, to eradicate this source wherever possible and to determine whether or not other people have been infected. This is often carried out in collaboration with other parties. This method is intended to prevent the further spread of an infectious disease. As well as the above tasks, it is the job of the GGD to advise both citizens and doctors about which measures need to be taken when an infectious disease occurs.

2.4 Medical microbiological laboratories

In a medical microbiological laboratory (MML), tests are carried out into the micro-organisms such as bacteria, fungi, yeasts, viruses and parasites, that can cause infections in humans. A number of different methods are available for this purpose, such as:

- identifying the pathogen by culture and isolation;
- demonstrating the presence of antibodies against the pathogen (serology);
- demonstrating the DNA of the pathogen through molecular techniques.

In a medical microbiological laboratory, the results of the tests are discussed between the microbiologist and the doctor who requested the tests.
The virology laboratory at the Erasmus Medical Centre in Rotterdam holds an unusual position because it is a reference laboratory that includes influenza testing; together with the RIVM it forms the National Influenza Centre (NIC).

2.5 National Institute for Public Health and the Environment

The National Institute for Public Health and the Environment (RIVM) is a centre of expertise and research institute that aims at promoting public health and a safe and healthy environment. The following core tasks of the RIVM, that are carried out in both national and international contexts, are intended to support governmental policies:

- policy support;
- national coordination;
- prevention and intervention programmes;
- providing information to citizens and health care professionals;
- developing expertise and research;
- providing support to regulatory bodies.

The RIVM is partly responsible for ensuring an independent and reliable flow of information to professionals and the general public alike on subjects such as health, medical drugs, the environment, food, and safety. The aim of the above is to utilize the scientific knowledge and skills of the RIVM as much as possible and to make them accessible to others.

Within the structure of the RIVM, various departments were involved with the control of the 2009 H1N1 pandemic. For example, employees from the Centre for Population Screening (CvB), Public Health and Health Services Division (sector V&Z) and Corporate Communications were all involved in the 2009 H1N1 pandemic.

2.5.1 Centre for Infectious Disease Control

The Centre for Infectious Disease Control (CIb) is one of four sectors within the RIVM. Nearly all of the activities at the RIVM relating to the prevention and control of infectious diseases fall collectively under the CIb. The CIb liaises with the regional GGDs, university research centres, medical microbiological laboratories and other relevant organizations. In addition, the CIb aligns its tasks with the ministries involved (e.g. Health, Welfare and Sport (VWS), Housing, Spatial Planning and the Environment (VROM), and Economic Affairs, Agriculture and Innovation (EL&I), and with national organizations (e.g. GGD Netherlands and the Netherlands Institute for Health Services Research, (NIVEL) that provide support to professionals. The CIb is also the liaison body for international organizations such as the European Centre for Disease Prevention and Control (ECDC) and the WHO. The CIb is subdivided into the LCI, EPI, RCP, LIS, LZO en BBA (see below for full names).

National Coordinating Body for Infectious Disease Control (LCI)
The LCI provides advice and support to doctors and public health nurses at the departments for infectious diseases control at the GGD. The LCI is the centre of expertise for the regional GGDs in the field of infectious diseases and provides them with up-to-date information on the prevention and control of such diseases. One of the main tasks of the LCI is to collaborate with professionals in daily practice for drawing up guidelines that can be used in practice for infectious disease control in the Netherlands. In addition, the LCI monitors the speed with which notifiable diseases are reported to the authorities. Should an outbreak or an epidemic of an infectious disease occur throughout more than one GGD region, then the LCI will coordinate the control response. The LCI also has the task of providing what is known as 'structure in a crisis' by setting up an Outbreak Management Team (OMT) for outbreaks of infectious diseases that spread over various regions or occur nationwide.

Department of Epidemiology and Surveillance (EPI)
In order to adjust the prevention and control policy in the Netherlands, it is essential that any changes in the prevalence of infectious diseases and related risk factors are detected as early as possible. As the organization responsible for the surveillance of infectious diseases, the CIb has a pivotal role in this. The investigations of the EPI are aimed at mapping the determinants of the spread of infectious diseases in the general population as well as evaluating the effects of interventions. The methods used for this purpose are surveillance and epidemiology including mathematical modelling. The EPI also keeps in contact with other European countries about surveillance, epidemiology and the effective control of infectious diseases.

The Regional Coordination Programmes
The Regional Coordination Programmes (RCP) bear responsibility for coordinating the implementation of the national vaccination programme. Among other things, the RCP sends invitations for participation in the National Vaccination Program (RVP). In addition, the RCP is responsible for the implementation of the screening of pregnant

women and newborn babies. The RCP has been part of the RIVM since January 2008; its tasks were previously carried out by the national and regional immunization administration centres. The RCP consists of teams in Bilthoven and five regional offices. The regional offices provide medical advice, supervise and distribute vaccines, immunoglobulins and test sets, make referrals to the clinical sector, pay the relevant institutions for their work, supervise medical treatments, and record the results of the programmes in a national database of medical dossiers. To perform its duties, the RCP is linked to municipal personal records databases.

Laboratory for Infectious Disease Diagnostics and Screening
The Laboratory for Infectious Disease Diagnostics and Screening (LIS) is responsible for providing laboratory support to meet the objectives of the CIb. To achieve this, the LIS performs patient-oriented and epidemiological diagnostics in the areas of bacteriology, virology, parasitology and mycology, surveillance and molecular epidemiology of antibiotic resistance, research on the immune status of pathogens and the monitoring of pathogenic populations and any changes that occur within them. The LIS is also responsible for performing laboratory tests that fall under the national screening programmes for pregnant women and newborn babies. Research at the LIS is aimed at augmenting the knowledge and expertise that is necessary for the control of infectious diseases. This includes the coordination of the laboratory tasks involved.

Laboratory for Zoonoses and Environmental Microbiology
The Laboratory for Zoonoses and Environmental Microbiology (LZO) investigates the risks that arise for humans and the environment from micro-organisms present in food, water, soil and the air. Based on the risk assessments that are made, the LZO issues advice on which measures need to be taken. This advice may lead to policy measures that reduce and maintain human exposure to pathogens at a low level.

Department of Policy, Operations Management and Advice
The Department of Policy, Operations Management and Advice (BBA) is responsible for a balanced and strategic research policy (research management), good commissioning and performance of work (account management) and for ensuring good internal coordination and collaboration. BBA also has tasks in the area of policy, steering, grant management and international collaboration. BBA stimulates new administrative developments relating to the infrastructure of infectious disease control. In addition, BBA ensures support of the operational processes in terms of line and project management in the areas of finance, contract formation, assurances for quality, occupational health and safety and environmental issues and information policies.

Regional Consultants Medical Microbiology and Regional Consultants Communicable Disease Control
Since 2006 the laboratory professionals referred to as COMer (regional consultants medical microbiology) and RACer (regional consultants communicable disease control) have been detached to the regional GGDs and the CIb in order to bridge the gap between the national and regional bodies working on prevention and control. Together with representatives of the central laboratories at the CIb, seven COMers make up the Committee of Diagnostic Microbiology (COM). The COMer's most important tasks are: to act as an intermediary for all laboratories in the region, to collaborate with the consultant infectiologist of the GGD, to act as a coordinator for the laboratories in any region where an outbreak occurs, and to perform contact investigation and advise the Regional Committee for Infectious Disease Control. The seven consultants are supported and managed by the COM Coordinator at the CIb.

In each of the seven regions there is also a RACer appointed for communicable disease control. The main tasks of the RACer are: to participate in and support the Regional Committee for Infectious Disease Control, to ensure the coordination in the event of any large outbreaks, to participate in periodic meetings at the CIb and to support other regions in national or large scale crisis situations.

2.5.2 Centre for Population Screening

The Centre for Population Screening (CvB) is part of the Public Health and Health Services Division (V&Z) at the RIVM. At the request of the VWS Ministry, the CvB directs and coordinates the national screening programmes such as the national influenza prevention programme. The actual screening is carried out by a large number of collaborating organizations. Within this collaborative effort, each individual organization has its own powers and responsibilities. The CvB ensures that the network of organizations involved in the various programmes is working optimally. As well as the role of director, the CvB has the following tasks: sets quality requirements, funds and controls the screening providers, monitors and evaluates, collates relevant knowledge and expertise and facilitates uniform public information. The collaborative efforts of the organizations and professionals involved in the population screening programmes contribute to a healthier population. The CvB is also involved in the preparation of new screening programmes and in developing and improving existing programmes.

2.6 Netherlands Vaccine Institute

The Netherlands Vaccine Institute (NVI) buys in vaccines and provides the vaccines needed for the Netherlands vaccination programmes and the yearly flu jab – the National Influenza Prevention Programme. In addition, the NVI is responsible for the purchase and distribution of antiviral agents and vaccines during a flu pandemic. The NVI is responsible to the VWS Ministry. Communication with the general public concerning antiviral agents and vaccines is effected through the Ministry. The NVI does not have its own tasks regarding communication with the general public.

2.7 Health Council of the Netherlands

The Health Council of the Netherlands (GR) is an independent scientific advisory body that provides the government and parliament with advice, usually but not always requested, on issues concerning public health. There are approximately two hundred members of the Health Council who all represent the various areas of research and/or the health care sector and who are appointed by Royal Decree. The council members produce advisory reports. For each advisory report, the Council members work ad hoc in independent committees made up of members who are specialized in that particular subject area assisted by experts who are not members of the Health Council. The advisory reports are tested by one of the seven consultation groups before being handed over to the Minister of VWS. The consultation group that is particularly relevant for the case in hand is that concerned with infection and immunity. As well as reviewing the draft versions of reports on infectious diseases, this group is a platform where developments can be highlighted and assigned importance.

For the area of infectious diseases, the Health Council will give its opinion, for example, on the draft guidelines that are drawn up by the Dutch Working Party on Infection Prevention (WIP); it will also assess the protocols (in use and/or updated) that have been drawn up by the LCI. The Health Council is also engaged in addressing specific questions related to infectious diseases. For example, they identify any relevant developments concerning the national vaccination programme

and also give recommendations for issues that may be related to a flu pandemic. In general, the work of the GR is based on requests from the Minister of VWS.

2.8 The Ministry of Health, Welfare and Sport

The national government has the constitutional task (pursuant to section 22 of the Constitution) of carrying out measures for the promotion of public health. The Minister of VWS is responsible for the way in which this is put into practice. This means that he is responsible for formulating the policy objectives and for deploying the instruments and actors needed to complete the process. He is also responsible for ensuring a targeted, effective and efficient implementation of the tasks. In the event of a pandemic, the Minister of VWS bears final responsibility for prevention and control policies.

2.9 The European Centre for Disease Prevention and Control

In 2005, the European Centre for Disease Prevention and Control (ECDC) was set up with the aim of identifying, assessing and communicating the risks to public health associated with infectious diseases to the Member States. So far, the ECDC has not had a role in the actual coordination of infectious disease control but has had an advisory and monitoring function vis-à-vis the participating countries. The EU Member States participate in a Network for the Surveillance and Control of Communicable Diseases that was initiated by the European Parliament. The aim of the network is to strengthen the prevention and control of infectious diseases in the EU by encouraging collaboration and coordination between the Member States with support from the European Commission. This network also contains a restricted online alert system called the Early Warning and Response System (EWRS) through which national public health authorities exchange relevant information on outbreaks and crises [1].

2.10 World Health Organization

The World Health Organization (WHO) is a specialized organization of the United Nations. The WHO was established on April 7, 1948. The objective of the WHO is to document the worldwide aspects of health care, to coordinate activities involved in health care and to promote the health of the world's population. Where infectious diseases are concerned, the WHO collates worldwide data, identifies outbreaks of infectious diseases and the onset of epidemics, provides announcements on incidents and up-to-date situations and provides coordination and concrete support when the prevention and control capacity of an affected country is inadequate. The WHO also played a pivotal role in the preparedness plans for this influenza outbreak. The WHO is supported in its work by professionals from many countries. Worldwide there are more than 8000 people working for the WHO in 147 district departments, 6 regional offices and the head office in Geneva, Switzerland.

International Health Regulations

The legal foundation for the WHO's activities is provided by the International Health Regulations (IHR) which the members of the WHO have undertaken to uphold. The IHR were renewed in 2005. Prior to this, the participating countries were required to report outbreaks of only three specified infectious diseases. The members widely support the obligation of notification, surveillance and coordination in the control of all infectious and highly contagious diseases – especially from the point of view of public health. Moreover, in many of its daily activities, the WHO no longer limits itself to just dealing with these three diseases alone. Also, international mobility has increased considerably since the original IHR were established. The current IHR came into force in 2007. The IHR describe the necessary sharing of information between the members and the WHO and oblige them to liaise through collaborative efforts.

The IHR contain health-related regulations for international trade and personal mobility as well as standards and measures that must be taken into account at international departure points and by international transport providers in a time of crisis; they also set out what other health documents may be necessary. The IHR give the members the right to take measures aimed at the protection of public health. The members may impose additional health measures as long as these will not have a detrimental effect on international trade and will not be more intrusive in respect of the mobility of persons.

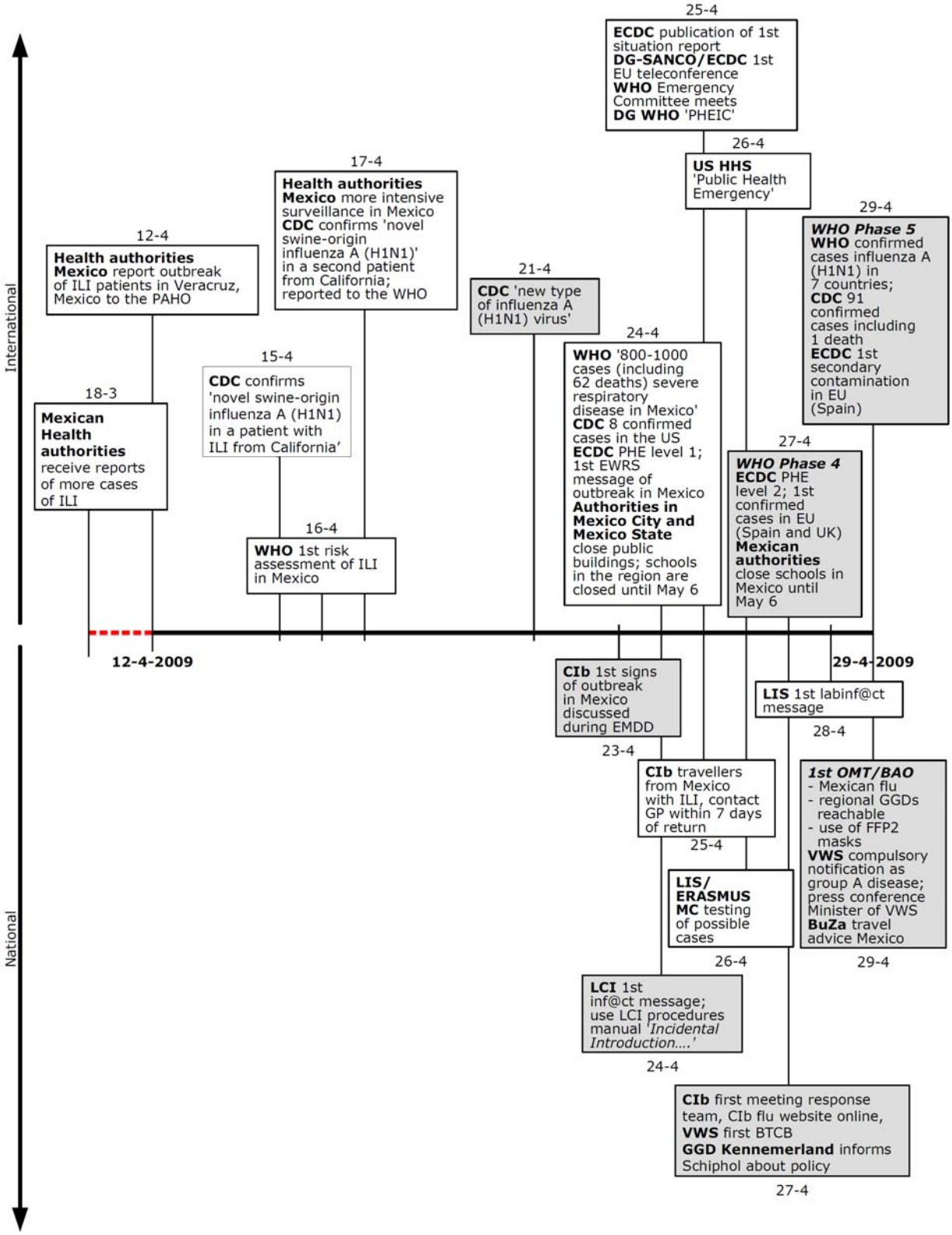

Figure 2 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period March 18, 2009 to April 29, 2009.

3 Period 1: from March 18, 2009 to June 29, 2009

Outbreak in Mexico and spread from Mexico, virus not yet present in the Netherlands.
On April 23, 2009 the CIb was confronted for the first time with the outbreak of a new type of influenza virus in Mexico. This chapter describes the spread of the new influenza virus from Mexico to the rest of the world up to the point at which the first case of 2009 H1N1 pandemic flu was confirmed in the Netherlands. At the time, not much was known about the exact nature and origins of the virus. Toward the end of this period, the WHO raised the level of pandemic alert to phase 5. All over the world, national health authorities were preparing themselves for the first reports of infected people. This was no different in the Netherlands, where numerous measures were being taken to prevent the new virus from spreading.

3.1 Situation

3.1.1 International

During March and early April 2009, an increasing number of patients with influenza-like illness were reported to the authorities in various parts of Mexico. Most of these patients had general flu-like symptoms such as fever, cough, and sore throat. However, some of these patients presented with a serious or acute respiratory infection and/or pneumonia. On April 12, 2009, the General Directorate of Epidemiology in Mexico reported an outbreak of influenza to the Pan American Health Organization (PAHO); it had occurred in a small community in the state of Veracruz. From April 17, 2009, following the death of a 39-year-old woman from an atypical pneumonia in the state of Oaxaca, the surveillance for influenza was intensified [2].

Influenza-like illness (ILI) is defined as an acute onset of fever (38 °C, symptoms appearing within 24-hours) and cough, sore throat, and/or chest pain.

On April 1, 2009, a 10-year-old Californian boy with asthma was examined and treated at an Emergency Department for symptoms of fever, cough and vomiting. The boy recovered from the illness within one week. A nose-throat swab was taken from this boy for testing as part of an evaluation study into diagnostic testing being conducted at that time. The sample showed an influenza A virus that could not be further subtyped. In accordance with the study protocol, the sample was sent to a reference laboratory for further investigation. In the reference laboratory, the sample tested positive for the influenza A virus but negative for the subtypes H1 and H3 of the human influenza viruses. On April 15, 2009, the American Center for Disease Control (CDC) received the clinical sample. The CDC concluded that this was a 'novel influenza A (H1N1) virus of swine-origin'. On the same day, the California Department of Public Health was informed by the CDC that a novel virus had been found [3].

On April 17, 2009, the CDC received a nose-throat swab taken from a 9-year-old girl, also from California, but who had no epidemiological link with the 10-year-old boy. The 9-year-old girl had started to show symptoms of fever and cough on March 28, 2009. Two days later she was treated in an outpatient department that was taking part in an influenza surveillance project. It was at this outpatient department that the nose-throat swab was taken and sent to the Naval Health Research Center in San Diego where an influenza A virus was identified but, again, could not be further subtyped. The sample was transported to the CDC where it was received and tested

on April 17, 2009. Once more a 'novel influenza A (H1N1) virus of swine origin' was confirmed. The gene type of the virus isolated from the 9-year-old girl's sample was comparable with the virus that had been isolated from the 10-year-old boy's sample. On April 17, 2009, the CDC reported these two cases to the WHO in accordance with the International Health Regulations (IHR). Epidemiological examination of the two patients revealed that neither had had any recent contact with pigs [3].

On April 21, 2009, the CDC published the cases of the two 'swine influenza A (H1N1) virus' infections in the two children from California in their Morbidity and Mortality Weekly Report (MMWR). The new virus was found to contain some genetic elements from two different types of swine flu viruses that were in turn found to be mixed with genes of avian and human influenza descent. At that point in time, it was not clear to the CDC whether the distinct reassortment that led to the novel virus had taken place in pigs or humans [4]. Initially, the virus was referred to as 'swine flu' because there was a strong suspicion that the primary source of contamination came from pigs.

On April 23, 2009, the laboratory of the Public Health Agency of Canada (PHAC) confirmed that further cases of severe respiratory infections in Mexico had been caused by an infection with the 'swine-origin influenza A (H1N1) virus'. Sequential analysis showed that the patients in Mexico were infected with the same type of 'swine-origin influenza A (H1N1) virus' that had been found in the two children from California. The clusters of cases with the 'swine-origin influenza A (H1N1) virus' infections in Mexico had been communicated to the PAHO [2].

On April 24, 2009, the WHO confirmed that patients with the 2009 H1N1 pandemic flu virus had been diagnosed in Mexico and in the US. The outbreak was causing clusters of infected patients with severe airway infections and/or pneumonia and was possibly also the cause of several deaths [A, April 24, 2009]. At this point in time, estimates of the number of possible cases of infection with the novel virus in Mexico varied from 800 to more than 1000 and 62 deaths had occurred that could be directly related to the effects of the 2009 H1N1 pandemic virus. At the time, there were 8 patients in the USA with a diagnosis of flu confirmed by laboratory tests; only 1 of these 8 patients had been admitted to hospital and none of them had yet died [B, April 25, 2009]. Moreover, none of the confirmed cases in the US had had any contact with pigs [B, April 26, 2009].

On April 26, 2009, the US Department of Health and Human Services (HHS) declared the outbreak of 2009 H1N1 pandemic 2009 a 'public health emergency' (PHE). This made it easier for various US health authorities to carry out their duties.

On April 27, 2009, the WHO raised the level of pandemic alert from phase 3 to phase 4. The decision to do this was primarily based on the epidemiological data and laboratory information that was available. The data reflected a persistent human to human transmission of a virus that had changed significantly compared with human influenza viruses; it was therefore probably not well recognized by the immune system [A, April 27, 2009]. On the same day, the first cases in the EU – occurring in Spain and the United Kingdom – were confirmed by laboratory tests. All of the confirmed cases were people who had recently returned from a trip to Mexico. It then came to light that 11 other EU Member States were doing virological tests on suspected cases of the 2009 H1N1 flu virus. Furthermore, there were more confirmed cases in the US (40) and in Canada (6). These cases were also mainly people who had returned from a trip to Mexico. All those people diagnosed outside Mexico had mild symptoms. In Mexico the first 5 deaths of confirmed cases of the 2009 H1N1 pandemic 2009 were reported; at this point it was estimated that more than 1600 people in Mexico could possibly be infected with the virus [B, April 28, 2009].

WHO influenza pandemic alert phases
In the event of a flu pandemic, the WHO works with a set of six alert phases. These phases are described as follows:

- Phase 1: low risk of infection of humans with the animal influenza virus.
- Phase 2: the animal virus is potentially a risk for infection in humans.
- Phase 3: human infection with a new virus that has not resulted in human to human transmission.
- Phase 4: small-scale human to human transmission of the new virus that is not yet fully adapted to humans.
- Phase 5: spread of the virus by human to human transmission in at least two countries within one WHO region. The virus is not yet fully transmissible.
- Phase 6: increased and sustained transmission of the virus in human populations in at least two WHO regions.

The WHO declares these alert phases worldwide. The phases are the guiding principle in the policy procedures manuals and operational procedures manuals that are used by the Dutch government.

From reports published by the ECDC on April 28, 2009, it became clear that the number of confirmed infected and possible cases in Europe was continuing to rise. Whilst the disease seemed to be more severe in Mexico than in other parts of the world, the ECDC advised close monitoring of the outbreak so that any changes in the virus characteristics could be identified as early as possible. This led to the expectation that the virus would become more manifest in Europe as soon as human to human transmission started [B, April 28, 2009].

One day later, on April 29, 2009, the ECDC reported the first possible human to human transmission in Europe. This was a case in Spain where someone had been infected by a household member [B, April, 29]. On the same day, the WHO raised the level of pandemic alert from phase 4 to phase 5 [A, April 29, 2009]. Phase 5 is characterized by spread of the virus through human to human transmission in at least two countries in one WHO region. The confirmation of human to human transmission in Mexico and the US was the reason why the WHO changed the alert phase. At that point in time, there were 91 confirmed cases in the US. In addition, there was a report of the first death as a direct result of the 2009 H1N1 flu virus in the US. This case was a young child from Mexico who had been treated in Texas for a medical condition other than flu. Moreover, in some patients in the US a more severe clinical picture was being seen than previously observed in cases outside Mexico. The CDC was bearing in mind the possibility that the 2009 H1N1 pandemic virus was not as mild as first reported. Up to that point, there had been 7 deaths in confirmed cases in Mexico.

3.1.2 National

On April 23, 2009, the first warning in the Netherlands was received at the CIb and discussed in the expert meeting for disease detection (EMDD). From that point in time, the international developments on the 2009 H1N1 pandemic were followed closely through the websites of the ECDC, WHO and CDC and reported weekly in the expert meetings and documented in the weekly summary of infectious disease detection.

Expert meetings for disease detection
At the CIb, expert meetings for disease detection are held on a weekly basis. The coordination, preparation and reporting of these meetings is done by the Department of Epidemiology and Surveillance (EPI). The objective of the meetings is to draw attention to and monitor an infectious disease that could pose an acute threat to public health. This is done by distributing information to all those involved. Various surveillance sources are consulted prior to the meeting. Discussion in the meetings centres on the following: any signs of disease that could be important in terms of public health, any increase in the prevalence of an existing disease or the emergence of a new infectious disease such as the 2009 H1N1 influenza. In addition, warning signs may reach the expert meeting through other sources, for example, through the participants' contacts in their own field of work or from consultants for communicable disease control at the regional Public Health Services (GGD) and/or clinical microbiologists. Those taking part in the expert meetings are: doctors, vets, microbiologists and epidemiologists from various departments of the CIb such as LIS, LZO, EPI, and the LCI. Vets from the Food and Consumer Product Safety Authority (VWA) are also present at the meetings. The outcome of the meetings is summarized in a report that is e-mailed to all people involved in infectious disease control in the Netherlands on the same day.

On the evening of April 24, 2009, doctors and nurses were sent the first message (through Inf@ct – see section 3.4.2 on communications) on how to respond to any suspected cases of 2009 H1N1 pandemic flu. Supplementary measures were recommended for people returning from a trip to Mexico. The LIS and EMC were ready and prepared to carry out diagnostic tests. In response to the advice given by the CIb, a great deal of media attention was given to the policy for patients returning from Mexico.

Up to and including April 29, 2009, there were no cases reported to the CIb of 2009 H1N1 pandemic flu in the Netherlands that had been confirmed by laboratory tests.

3.2 Diagnostics

3.2.1 International

On April 21, 2009, the CDC gave the first announcement that this disease was a new strain of the influenza A H1N1 virus. The sequential analyses showed that the new virus had genetic elements of swine flu viruses but also of avian and human flu viruses. The only clear link to pigs was the gene sequence but there was no surveillance for influenza in pigs in Mexico or elsewhere, which meant that the actual source of the virus was still not clear. The CDC laboratory tests also showed that the virus was naturally resistant to the antiviral drug amantadine, but sensitive to neuraminidase inhibitors such as oseltamivir and zanamivir [4]. On April 24, 2009, the sequences were released through the influenza network of the WHO. Having access to this information meant that scientists around the world could develop the primers and probes for the Polymerase Chain Reaction (PCR) – a necessary technique for detecting a virus in nose-throat swabs [E, April 26, 2009]. On April 28, 2009, the CDC published the real-time PCR protocol (RTPCR) and a kit became available for the Dutch National Influenza Centre (NIC).

In the period up to April 29, 2009, the ECDC was working on a uniform case definition for Europe.

3.2.2 National

On April 27, 2009, a case definition was determined in the Netherlands by the CIb [C, April 27, 2009]. The case definition contained the clinical and epidemiological criteria

upon which further diagnostic testing could be based. These were the clinical and epidemiological criteria for determining whether or not laboratory diagnostics are needed in patients suspected of infection with the 2009 H1N1 pandemic virus.
From April 27, 2009, the following case definition for a possible case of infection was used in the Netherlands:

- fever > 38.5 °C with symptoms or signs of acute respiratory infection;
  or
- severe pneumonia;
  or
- death resulting from an unexplained acute respiratory infection.

AND with onset of illness within 7 days of:

- contact (< 1 meter) with a person in whom infection with the 2009 H1N1 virus had been confirmed when that person was ill;
  or
- contact (< 1 meter) with animals in which infection with the 2009 H1N1 virus had been confirmed;
  or
- a trip to an area where the 2009 H1N1 pandemic flu was present. Up to April 28, 2009, this only applied to travellers returning from Mexico after April 17, 2009;
- after April 28, 2009, this only applied to patients who developed fever and other symptoms within 7 days of returning from Mexico. Considering that the estimated incubation time was 7 days, there was no point in going further back in time.

Case definitions for a probable and a proven case

From April 27, 2009 the following definitions were in place in the Netherlands.

- Probable case: every person who meets the criteria of a possible case accompanied by a positive laboratory test result for an influenza A virus that could not be further subtyped.
- Confirmed case: a person who meets one of the following laboratory criteria for confirmation:
  - 2009 H1N1 pandemic virus present in clinical material RTPCR or virus culture (BSL-) (BSL-3);
  - a neutralizing antibody response to the 2009 H1N1 pandemic virus with four-fold increase in titers between the acute phase serum and the sample taken 10-14 days later.

In the Netherlands, the Laboratory for Infectious Disease Diagnostics and Perinatal Screening (LIS) and the Erasmus Medical Center (EMC) collectively form the National Influenza Center (NIC). From April 24, 2009, both laboratories were using the LCI procedures manual *Operational Procedures Manual for Incidental Introduction of a New Human Influenza Virus in the Netherlands*. Samples taken from suspect cases were tested simultaneously in both laboratories, in accordance with agreements made within the context of the WHO. This was done because when a new virus occurs, it takes some time before it is known how effective the available laboratory methods work with this new virus – this is known as validation. For the diagnostic tests, a broad spectrum detection method using real-time PCR was used that can detect all types of influenza A viruses. This method had also been validated by the NIC for the diagnostic testing of seasonal influenza. Because of this, it was recommended for use in all diagnostic centres in the Netherlands. This was considered sufficient reason for many laboratories to use the method. However, the method does not differentiate between various subtypes of influenza A virus except when the virus is sequenced – which did take place for the initial cases. In order to differentiate between the 2009 H1N1 pandemic virus and, for example, the normal A H1N1 seasonal influenza, new real-time PCRs were developed based on information

from the WHO [5]. Because there was no positive control material available, viruses from pigs were used as reference material.

During the weekend of April 25-26, 2009, the first samples from possible cases were examined at the LIS and the EMC following an indication issued by the LCI. All of the samples up to that point had tested negative. On April 29, 2009, the new tests that had been developed specifically for the 2009 H1N1 pandemic virus became operational (H1 RIVM and N1 (EMC)). In addition, the LIS started to organize the necessary scaling up of laboratory services with nine selected laboratories (outbreak assistance laboratories) in the Netherlands. On April 28, 2009, the CDC published the real-time PCR protocol (RTPCR) and a kit was made available to the NIC network. A decision was made to order primers and probes from this kit and, together with the quality control panel, to have the outbreak assistance laboratories (OAL) test them against their own protocols [6]. All actual diagnostic testing was still being carried out at the LIS and EMC [E, April 29, 2009].

The outbreak assistance laboratories (OAL) are nine virology laboratories in the Netherlands that together with the LIS and EMC took measures to ensure the implementation of diagnostic tests specially designed for the 2009 H1N1 pandemic virus [6]:

1. Academic Medical Centre Groningen;
2. Laboratory for Infectious Diseases Groningen;
3. Academic Medical Centre Amsterdam;
4. Leiden University Medical Centre;
5. Academic Medical Centre Utrecht;
6. Radboud University Nijmegen Medical Centre;
7. Regional Public Health Laboratory, Tilburg;
8. Multidisciplinary Laboratory for Molecular Biological Diagnostics in Den Bosch;
9. Maastricht University Medical Center.

From April 2009 the LIS was supported in its tasks by the Epidemiology and Surveillance Unit (EPI). Assistance was given for updating the collective LCI/LIS logbook (see Control, section 3.3.2), dealing with the requests for diagnostic tests (in LIMS), and drawing up the instructions for the regional Public Health Services (GGD) for the taking of and sending of samples.

Triage structure (diagnostics)

During routine diagnostic testing, requests for tests and samples are sent directly to the laboratory and the results are sent back to the department/person who requested them, for example, GPs, hospitals. However, during a major outbreak and particularly in the early phase of a pandemic (contamination phase) the requests for diagnostic tests are communicated through the Public Health Services (GGD) who then further communicate with the LCI. The LCI assesses the indication for further testing based on the case definition criteria and passes this on to the LIS. The samples are transported directly to the LIS for subtyping and sequencing where they are divided up with some parts being sent to the EMC (reference laboratory LIS) for parallel testing of the samples. The LCI is informed as soon as the results from both laboratories are known. Subsequently, the LCI reports back to the GGD which in turn informs the patient and the GP concerned [7]. An outline of the management processes surrounding a new case or suspected case of 2009 H1N1 pandemic flu in the early stage of a pandemic is set out below.

Management of a suspected or confirmed case of 2009 H1N1 pandemic flu

- If a GP, doctor or specialist reports a case of suspected 2009 H1N1 pandemic flu to the GGD, then the GGD will assess the presence of clinical and epidemiological criteria and decide whether to approach the LCI for an indication for further assessment by laboratory diagnostics.

- If the LCI is approached by telephone by the GGD, then the LCI will decide whether or not to give an indication for laboratory diagnostics on the basis of the case definition and the patient's details.
- In the event that a case was indicated by the LCI for laboratory diagnostics, then samples would be taken from the patient and any contacts of the patient who had clinical symptoms. The samples were sent from the GGD to the LIS and on arrival there were registered in LIMS (see Control, section 3.3.2). The samples were divided up at the LIS with some parts being sent to the EMC reference laboratory.
- As soon as the results from both laboratories (LIS and EMC) were known, the LCI would be informed. At the LCI, the doctor on duty would then assign the cases so that the various GGDs could be informed – this was done with the help of a telephone list. Both positive and negative results were communicated in this way. The GGD then contacted the patient and his/her contacts. The GGDs would also take samples from the contacts of positive cases and these samples would then again be sent to the LIS for testing. During the pandemic, the data collection for novel influenza A (H1N1) cases was processed in various systems (see Control, section 3.3.2).

Cases of mismatch of patient details
The patient samples were sent to the LIS by the GGD. The LIS subsequently attached the result of the laboratory diagnostics to the patient information that had been collected by the LCI. However, the samples were often not correctly labelled by the GGDs with the correct identifiers (BSN number, postal code and birth name) which meant that the LIS had problems linking the results to the LCI registered case. Consequently, the LIS and the LCI had to contact the GGD concerned separately before they could link the information and then subsequently inform them of the results.

Making laboratory results known during the first stage of the pandemic
During the first stage of the outbreak of 2009 H1N1 flu, the samples were tested by LIS as soon as they had been received. This meant that the laboratory results could only be passed to the LCI between 6 and 8 o'clock in the evenings. So, the GGDs could only be informed by the LCI after this time and they then had to contact the patients concerned and their contacts. Up until mid June 2009, the regional GGDs were taking appropriate action in the evening hours but after this time, due to the practicalities of this practice, the patients and their contacts were contacted the following morning. From May 11, 2009, the LIS started to perform 1 set of tests each day – samples that had been received before 11 in the morning were included in that day's diagnostic testing round. This meant that the laboratory results were available earlier in the day.

3.3 Control

3.3.1 International

In Mexico, drastic measures were taken to stop the new virus from spreading from April 24, 2009 onwards. Travellers entering and leaving the country through Mexican airports were informed about the outbreak and advised to seek immediate medical advice from their GP if they developed any influenza-like symptoms. In addition, a large national publicity campaign was started, major public events in Mexico City were cancelled and schools were closed until May 6, 2009, affecting 7.5 million children and students in Mexico City and the federal state of Mexico. The Mexican authorities advised people to wear masks, wash their hands with soap and to stay away from people with respiratory problems. The Mexican borders were not closed [B, 25/26 April 2009]. On April 27, 2009, the Mexican government decided to close all schools in Mexico until May 6, 2009.

In the US, the standard precautionary measures for respiratory hygiene and cough etiquette were taken for people with flu symptoms. No travel restrictions were imposed by the US. The CDC did make an outbreak announcement to warn travellers about the increasing health risk in Central Mexico and Mexico City [B, April 26, 2009]. At the end of April 2009, some schools in New York (US) were closed for at least seven days because of the 2009 H1N1 pandemic virus [B, April 29, 2009].

On April 28, 2009, the Director-General (DG) of the WHO announced that there had been an extensive spread of the new virus. Global containment of the outbreak was no longer feasible and the focus therefore shifted from containment to mitigation measures [A, April 28, 2009]. In Europe, the ECDC communicated documents to the EU Member States containing policy measures for travellers (and their contacts) to and from Mexico and the US. The ECDC reported that all the EU Member States had taken the necessary control measures to prevent the virus from spreading in Europe [B, April 28, 2009].

Before the outbreak of 2009 H1N1 pandemic flu, the ECDC had pointed out the importance of an analysis of the first few hundred cases (FF100) should a pandemic occur. Analyses of these first cases of influenza can provide information on issues such as the severity of the disease. Such analyses are essential for establishing the control policy at national and European level. Many countries have indeed performed such an analysis – including the Netherlands[5].

3.3.2 National

From April 24, 2009, the advice given to professionals in the Netherlands (through Inf@ct) was to use the LCI procedures manual: *Incidental Introduction of a New Human Influenza Virus in the Netherlands*. This procedures manual contains detailed information on the taking and transporting of samples, registration forms and outlines the required measures for isolation at home, at the GP surgery and in hospital. At this point, the aim was to detect cases of the 2009 H1N1 virus early on and thus prevent further spread of the virus in the Netherlands as much as possible. People who met the clinical and epidemiological criteria were requested to contact their GP for a clinical assessment. Infected patients were asked to stay at home in isolation for as long as their clinical condition allowed this. Initially, this only concerned people who had travelled from Mexico. The patients who met the criteria of the case definition were given oseltamivir as treatment; their contacts were given oseltamivir as a prophylactic and also a mask – as stipulated in the procedures manual [C, April 24, 2009].

National procedures manuals LCI
Procedures manuals were drawn up by the LCI as part of the preparedness plan for a possible pandemic of the 2009 H1N1 influenza virus. The procedures manuals describe which measures have to be taken when a certain situation occurs. The procedures manual *Incidental Introduction of a New Human Influenza Virus in the Netherlands* was written for the WHO pandemic alert phases 4 and 5. The procedures manual *Control of an Influenza Pandemic* was written for the WHO pandemic alert phases 5 and 6. This manual contains information on the use of antivral agents and the vaccination strategy.

In addition, as part of the preparedness plan, the procedures manual *The Consequences of Avian Influenza for Public Health* was written and intended for use as a guideline for fighting the consequences in humans of avian influenza in poultry.

Diagnostic testing could be carried out after consultation with the GP concerned and the local GGD. The GGD assessed the presence of clinical and epidemiological criteria

and decided whether or not to contact the LCI for an indication for further diagnostics. Based on the case definition, the LCI would determine whether or not diagnostic testing should take place. The GGD made agreements with the treating physician for taking the samples. The GGDs were responsible for taking the samples. A PowerPoint presentation for professionals was put on the CIb flu website with additional information on the methods for taking samples [C, April 25, 2009]. On April 27, 2009, through an Inf@ct message, the LCI recommended the wearing of FFP2 masks and gloves when taking samples. However, this message was changed the same day to one saying that wearing an FFP1 mask and gloves was sufficient [C, April 27, 2009].

Issuing of antiviral agents or drugs
The treating physician or GP decided whether antiviral agents were indicated and prescribed the drugs by writing out a prescription for the patient's regular pharmacy. If prophylactics for contacts were deemed necessary for contacts, then these were prescribed in the same manner. If, for any reason whatsoever, the supply of antiviral agents at the pharmacy was not sufficient, then the physician could apply for antiviral agents to be released from the government's national store which contained 5 million courses of oseltamivir. The treating physician could make a request through the GGD to obtain these drugs with the help of the duty physician at the LCI. Supplies are only taken from the national store when strictly indicated. The GGD issued tablets to those people who were eligible. The final responsibility for the government's supply of oseltamivir in the national store lay with the Minister of VWS. VWS and the NVI had made agreements on managing the supply. The logistics surrounding the supply of antiviral agents were regulated by the NVI [8].

On April 27, 2009, the WHO raised the level of pandemic alert to phase 4 and two days later this was raised to phase 5. These actions had few practical consequences for the control of the virus in the Netherlands. The procedures for diagnostics and precautionary measures did not change and neither did the case definition. However, the policy surrounding personal protective measures did change again within a short space of time. Health care workers who came into contact with a patient with a suspected or confirmed case of 2009 H1N1 pandemic infection were advised to take the following protective measures.

- FFP2 mask;
- gloves;
- gown;
- goggles;
- hand disinfection.

Patients in hospital had to be placed in strict isolation [C, April 28, 2009].

At the end of April 2009, the GGD for the municipality of Kennemerland provided Schiphol airport with information on the policy with regard to travellers returning from Mexico. For this purpose, the GGD compiled imformative letters which were handed out to passengers going to and returning from Mexico. In these letters, travellers were advised to seek medical advice from their GP if they developed a fever higher than 38.5 ºC. In addition, posters were displayed at Schiphol – and later at other Dutch airports – with information in five languages on the hygiene measures that should be taken.

From April 29, 2009, the Ministry of Foreign Affairs advised against any unnecessary trips to Mexico in connection with the outbreak of 2009 H1N1 pandemic flu in Mexico. People who had to go to Mexico were advised to exercise caution on the following points:

- to avoid contact with people who have the flu;

- to take general hygiene measures seriously;
- to keep an eye on the local situation as well as any changes to existing advice;
- to see a doctor if signs of illness develop – e.g., fever higher than 38.5 ºC et cetera.

The LCI and LCR advised against prescribing oseltamivir as a preventive therapy for travellers going to Mexico [C, April, 29, 2009].

Airports
During a pandemic, international air traffic helps a virus to spread more quickly. In the national procedures manual, in the section on communication to the public, it is stated that travellers must be duly informed through flyers and posters that are distributed by the regional Public Health Services. The Ministry of Infrastructure and the Environment helps with the logistics needed for this task.

On April 29, 2009, the Minister of VWS announced that cases of 2009 H1N1 pandemic flu were notifiable as a group A disease. This meant that every patient suspected of being infected (possible case) had to be reported immediately to the GGD if the patient met the clinical and epidemiological criteria of the case definition. The GGDs were responsible for registering the patients in Osiris and were requested to fill out the Osiris questionnaire. Osiris is an electronic database used by the regional GGDs for registering notifiable diseases. All doctors and heads of laboratories registered under the Individual Healthcare Professions Act [*Wet BIG*] received a letter from the RIVM about the inclusion of the 2009 H1N1 pandemic influenza virus as a group A disease falling under the Public Health Act. This letter was delivered in week 20 of 2009 [E, May 8, 2009].

Including the 2009 H1N1 pandemic virus as a group A disease meant that as soon as this had been done, the management of the outbreak could be steered by the Minister of VWS. Besides placing the patient in isolation, this meant that the patient's contacts could also be placed in quarantine [C, May 4, 2009].

Data collection for cases of 2009 H1N1 influenza infection was processed in various registration systems during the pandemic.

Osiris
Notifications of cases and possible cases of infection with the 2009 H1N1 virus were registered by the GGDs in the electronic database called Osiris that is used for the notification of notifiable diseases. Through patient material and questionnaires, the GGDs collected information on the following: demographic characteristics, medical history, symptoms, primary and/or secondary care, exposure, possible country of transmission, contacts and diagnostic data. The names and details of possible patients who had consulted their GP were passed on to the GGD in the relevant region. Osiris was used to record cases of the 2009 H1N1 pandemic virus from April 29, 2009, onwards. During the first stage of the 2009 H1N1 pandemic outbreak, both possible and confirmed cases were registered in Osiris by the GGDs.

LIMS
The Laboratory for Infectious Disease Diagnostics and Perinatal Screening (LIS) has its own laboratory information management system (LIMS) in which every sample is recorded before it is tested. This system contains detailed information, such as whether or not someone has been vaccinated for seasonal flu, use of prophylactics, possible country of transmission and first day of illness.

LIS/LCI logbooks
From April 25 to June 29, 2009, a collective data file (logbook) in Microsoft Excel® was used and maintained by the LCI and the LIS with support from the Department of Epidemiology and Surveillance (EPI). This logbook records the following information:

- personal data, case studies and contacts (the so-called identifiers: BSN number, postal code and birth name);
- date of first day of illness;
- symptoms of case;
- GGD doctors involved;
- yes/no indication for further diagnostics;
- results of diagnostic tests.

The LCI collected patient data for the logbook. This patient data was collected during the registration process from the GGD. If a case tested positive by the LIS, then the LCI would request additional patient data from the GGD. Due to the increase in the number of positive cases of 2009 H1N1 infection at the beginning of June 2009, the additional exchange of data that took place between the GGD and the LCI for a confirmed case was standardized with the introduction of a special 'patient data' form. This form was in fact a check list for data that had to be systematically documented so that source and contact investigation could take place and also to collate data on confirmed cases that the EPI had to pass on to the WHO.

One practical disadvantage of the collective Excel logbook was that only one person could access the data at any time. To get around this, with the help of Microsoft Office Access® the LIS arranged for the LCI to have a separate input screen so that the LIS could access and add the laboratory results to the information.

3.4 Government communications

3.4.1 International

In the early stages of the outbreaks in Mexico, the Mexican national health authorities were the most important source of information for international institutions such as the WHO and the ECDC. In spite of this, the severity of the situation in Mexico remained unclear for a long time. This meant that the number of reported outbreak cases in Mexico varied greatly [A, April 24, 2009; B, April 25, 2009].

On April 16, 2009, the WHO communicated their first risk assessment for flu outbreaks in Mexico through the *Event Information Site* [A, April 16, 2009]. However, this risk assessment was revised on April 24, 2009 after contact had been made with the national health authorities in Mexico and the PAHO/WHO representation in Mexico. The situation in Mexico proved to be more serious than had been expected, leading to the first confirmed cases outside Mexico – in the US [A, April 24, 2009]. On the same day, the ECDC made the first announcement about the flu outbreaks in Mexico through the Early Warning and Response System (EWRS). EWRS is a closed communication system for the European Member States.

On April 25, 2009, the ECDC published their first situation report, thus sharing the information on epidemiological situations, control measures and other related information on the 2009 H1N1 pandemic with the EU Member States [B, April 25, 2009]. These situation reports were partly based on information concerning confirmed cases that had been reported through the EWRS by the Member States themselves and by European Free Trade Association (EFTA) countries [B, May 1, 2009].

On April 27, 2009, the first set of Frequently Asked Questions (FAQ) on the outbreak of the 2009 H1N1 pandemic was published by the ECDC [B, May 17, 2009]. From April 29, 2009, the new virus was named 'Influenza A (H1N1)' by the WHO.

The ECDC situation reports were based on reports from EU Member States and EFTA countries. The number of confirmed cases reported, for all countries except the US, was based on laboratory confirmation. However, the actual number of 2009 H1N1 flu cases could have been much higher than the number given in the ECDC situation reports. The account given by the ECDC was in part dependent on the national virological testing capacity and the policy of a particular country. In addition, there are many other reasons (for example, flu patients who don't consult their GP and are therefore not reported) that can be cited for the discrepancy between numbers reported and actually existing [B, May 27, 2009].

3.4.2 National

On April 23, 2009, the first signs of the 2009 H1N1 pandemic were described in the CIb's report of the weekly expert meetings for disease detection. From that moment onwards, the international developments were followed closely through the websites of the ECDC, WHO and CDC and reported and documented in the weekly summary of infectious disease detection.

In the Netherlands, the first message on the outbreak of 2009 H1N1 pandemic was sent via Inf@ct on April 24, 2009. This message informed people that swine flu had been confirmed in people in Mexico and the US (California) and referred them to the national procedures manual. For up-to-date information on the outbreaks, they were asked to consult the WHO and the ECDC websites [C, April 24, 2009].

On the evening of April 24, 2009, the first request arrived at the EPI from the CDC – the 'Swine flu modeling request' which came via the American Models of Infectious Disease Agent Study (MIDAS), a project in which the CIb was participating. Subsequently, on April 28, 2009, in collaboration with the MIDAS project team, the first estimate was made of the number of infected cases in Mexico [9].

Inf@ct is an electronic message service on infectious diseases and is run by the LCI
This service started in 2001 in collaboration with the Netherlands Association for Infectious Diseases (VIZ) and the Dutch Society for Medical Microbiology (NVMM). Inf@ct enables the following professional groups to receive and send messages on developments or incidents of infectious diseases quickly:

- doctors and nurses working on infectious disease control at the Regional Public Health Services;
- clinical microbiologists (members of the NVMM);
- Infectious disease specialists (members of VIZ), hygienists (members of Dutch professional association of hygienists VHIG).

During a crisis, Inf@ct also ensures that the LCI can communicate quickly and effectively with all parties involved. Furthermore, those on the Inf@ct network can, if they so wish, pass on any relevant information from the messages on Inf@ct to inform their own network of colleagues. The provision of information for other professional groups – both in and out of hospital – and that for individual GPs is not effected through Inf@ct [C, May 11, 2009].

Labinf@ct is a message service comparable to Inf@ct but intended for the further exchange of information relevant to laboratories. This message service was developed at the request of the regional consultants medical microbiology (COMers) and was used for the first time during the

outbreak of 2009 H1N1 flu. To make people aware of the system, all NVMM members received a letter from the chairman stating that all information on the 2009 H1N1 flu virus would be communicated through Labinf@ct.

From April 24, 2009, the homepage of the RIVM was updated daily with the latest news on the outbreak of 2009 H1N1 pandemic flu.

RIVM-com is used in this chronological summary to refer to the RIVM departments of Corporate Communication and CIb-Communication

At the onset of the 2009 H1N1 pandemic, an external consultant was called in to help RIVM-com in their many different communication activities. During the outbreak of the 2009 H1N1 pandemic, RIVM-com's tasks included the following:

- Continually updating the FAQ on the RIVM website as the real situation changed.
- Organizing press conferences at the RIVM.
- Writing letters and news reports for the RIVM website.
- Daily discussions with the communication advisors of relevant stakeholders, such as the Ministry of VWS.
- Writing and streamlining of background memorandums and leaflets.
- Setting up and updating the NVI website on vaccination.

During the entire pandemic, RIVM-com contributed to the development of all the information material drawn up by the VWS Ministry and the RIVM by reading it critically.

From April 27, 2009, professionals as well as the general public could visit the CIb's flu website for up-to-date information on the 2009 H1N1 pandemic virus (www.rivm.nl/cib/varkensgriep). On this special site the following items could be found:

- a daily bulletin with up-to-date information;
- news reports;
- updates on new developments;
- links to the WHO and the ECDC websites;
- the Dutch guidelines which were regularly updated;
- information for professionals on sample-taking, diagnostics et cetera;
- the most Frequently Asked Questions and answers (FAQ) These FAQs were revised on the basis of questions from daily practice and developments taking place worldwide.

The information for the public on the RIVM website was also updated during bank holidays [C, April 27, 2009]. Information for travellers was placed on the National Coordination Centre for Travellers (LCR) website [C, April 29, 2009].

On April 28, 2009, the first Labinf@ct message was sent which brought laboratories in the Netherlands up to date with the developments and procedures surrounding the 2009 H1N1 pandemic virus that were relevant to them. The RIVM maintained intensive contact with other national influenza centres in Europe (through the *Community Network of Reference Laboratories for Human Influenza in Europe*), the WHO (*Global Influenza Surveillance Network*) and national veterinary institutes on the subject of the latest developments on diagnostic testing of the virus worldwide [D, April 28, 2009].

On April 28, 2009, it was decided that any announcements or other news messages of confirmed cases in the Netherlands should be made by the RIVM and the Ministry of VWS and not by individual regional GGDs. This was because confirmation of a case

of the 2009 H1N1 pandemic virus in the Netherlands could potentially cause a lot of media and administrative attention [C, April 28, 2009]. One day later the LCI requested the regional GGDs to also make themselves available to professionals and the general public at the weekends and on bank holidays. Furthermore, the GGDs were advised to make arrangements for answering questions from the public, to prepare for scaling up as and when necessary, and to monitor the Inf@ct messages outside of office hours [C, April 29, 2009].

On April 28, 2009, the NIC drew attention to the 2009 H1N1 pandemic virus for the first time in their newsletter *Influenza Surveillance* (Nieuwsbrief Influenza-surveillance 2008/2009 volume 17, no. 9). This newsletter, whose title translated to: *New human influenza from pigs has appeared in Mexico and the US,* gave a detailed report on the situation in Mexico and the findings of the CDC.

The National Influenza Centre (NIC) is part of the WHO influenza network. The WHO network of NICs was set up for influenza surveillance, providing evidence for vaccine policy, preparing for outbreaks and pandemics and giving advice to professionals. The tasks of the NIC in the Netherlands are carried out by EMC and the CIb and their roles and specific tasks are set out in a contract. The director of the NIC is Professor Ab Osterhaus. Contractual tasks include determining the characteristics of viruses found during the monitoring that takes place in collaboration with the NIVEL- GP network, and of viruses isolated in diagnostic laboratories. The task of responding to outbreaks of disease is regulated by the CIb.

On April 29, 2009 a summary of the most important information on the 2009 H1N1 pandemic virus that was relevant to international travellers, was published on the CIb's flu website in English and Spanish.

On April 29, 2009, the Ministry of VWS held the first press conference on the outbreak of 2009 H1N1 pandemic flu. Minister Klink (VWS) indicated that there was no reason for concern and that all the required preparations had been made in the Netherlands. 'There is no reason for panic, although alertness and watchfulness are necessary', the Minister said [F, April 29, 2009].

3.5 Meetings

3.5.1 International

On April 25, 2009, the Directorate General for Health and Consumer Affairs (DG-SANCO) collaborated with the European Centre for Disease Prevention and Control (ECDC) and WHO Europe and held the first EWRS/Health Security Committee (HSC) teleconference during which the situation and the international measures surrounding the outbreak of the new virus were discussed with the EU Member States. The LCI and VWS also participated in this teleconference. The teleconference participants were given information about the following:

- use of the secure websites of Hedis and DG-SANCO for searching for information and updates;
- the GHSAG meeting organized to obtain information on the measures taken in non-EU countries;
- the increase of the HEOF activities to level orange.

It was agreed that a daily EWRS/HSC teleconference would be held [J, April 25, 2009; C, May 4, 2009].

On the same day, a meeting of the WHO Emergency Committee took place. Following this WHO meeting, the DG-WHO declared that according to the IHR, the current

situation was a 'Public Health Event of International Concern' (PHEIC) [B, April 26, 2009].

On April 29, 2009, the WHO organized an ad hoc scientific teleconference on the 2009 H1N1 pandemic situation. More than 100 people took part in this conference representing all the WHO regions. The objective of this meeting was to gain insight into the situations in the countries concerned and to share the available epidemiological, clinical and virological information [B, June 29, 2009].

On April 30, 2009, the Ministers of Health from the EU countries met in Luxembourg for an extraordinary session.

3.5.2 National

From April 27, 2009, the CIb's response team held daily meetings. Immediately following the meetings of the response team, the further procedure was brought into line during a telephone conversation with the policy officials of the Ministry of VWS [7]. This outcome was then used by the Ministry as input for the meetings of the VWS policy team for crisis containment (BTCB), which also took place on a daily basis from April 27, 2009. To start with, BTCB meetings were being held twice a day.

The response team at the CIb convenes when tackling a problem concerning a communicable disease requires input from more than one CIb department, making coordination by the LCI a prerequisite (see also CIb response plan). The response team consists of the director of the CIb, who acts as chairman, the heads of the CIb departments, the LCI duty doctor for infectious disease control, communication staff from RIVM-com and an LCI policy worker. The response team for the outbreak of 2009 H1N1 pandemic flu had a standard agenda which included the following points:

- International situation: number of cases worldwide, number of cases in Europe, striking increase in patients in one country, unusual cases and also important international publications.
- National situation: number of cases, unusual clusters, new policies to be determined, applicable for example to schools, signals from daily practice and control bottlenecks.
- Diagnostics: capacity of the LIS, collaboration with EMC, resistance testing, capacity of the OALs to scale up operations, logistics and relevant virological information.
- Communication: assignment of spokespeople, FAQ, website, radio and television appearances, articles in the newspapers, and journal publications.

The first Outbreak Management Team (OMT) meeting took place on April 29, 2009 and was immediately followed by the Administrative Consultative Committee on Infectious Diseases (BAO) meeting [G, April 29, 2009]. The first OMT meeting gave rise to the following recommendations [G, April 29, 2009]:

- The OMT recommended keeping to one clear nomenclature for the influenza virus, this was agreed as 'Mexican flu'.
- The OMT recommended supplementing the supply of oseltamivir in the event of its large-scale use, for example, during a higher pandemic phase.
- The OMT recommended updating the oseltamivir distribution plan.
- In the opinion of the OMT it was unlikely that administration of the seasonal vaccine would offer protection against infections with the 2009 H1N1 pandemic virus. The OMT did not recommend using the vaccine for people travelling to Mexico.
- The OMT advised the Minister of VWS to instruct the NVI to commence consultation with vaccine producers for a vaccine for the 2009 H1N1 pandemic virus.

- The OMT also recommended that the Medical Assistance Services for Accidents and Disasters (GHOR) update their procedures manuals.

The BAO approved all of the recommendations outlined above [H, April 29, 2009].

The Outbreak Management Team (OMT) is a consultation group that convenes in an impending crisis situation. Depending on the kind of outbreak, the participants of the OMT are drawn from GGD consultants for communicable disease control, clinicians, researchers, medical microbiologists and virologists, general practitioners and occupational physicians. During an OMT the international and national situation is outlined and the findings of laboratory tests and epidemiological analyses are presented. After this, the substantive discussions begin. Based on the outcomes of the OMT, recommendations are issued to the Minister of Health, Welfare and Sport (VWS) to continually adapt response to the disease control as the epidemiological situation changes. The OMT does not advise the Minister of VWS directly but through the Administrative Consultative Committee on Infectious Diseases (BAO) whose meetings are held immediately after the OMT meetings [7].

The Administrative Consultative Committee on Infectious Diseases (BAO) has the task of evaluating the recommendations of the OMT as to administrative compatibility, practicality and feasibility and to inform the Minister of VWS on this. The BAO is chaired by the Director-General of Public Health. Also participating in the BAO are the director of the CIb and representatives of the Public Health Directorate of VWS, the Dutch Health Care Inspectorate (IGZ), the Board of Directors (comprising 13 mayors) of the GHOR, the Public Health Services (GGD NL) and the Association of Netherlands Municipalities (VNG). If it is necessary, the BAO can be extended, for example with representatives of the Food and Consumer Product Safety Authority (VWA). The Minister of VWS makes his decisions after consulting with the BAO. The Director-General of Public Health is authorized by the Minister to take these decisions.

The OMT and BAO primarily bring out recommendations to VWS. Should other ministries – for example, the Ministry of Economic Affairs, Agriculture and Innovation (EL&I), Ministry of the Interior and Kingdom Relations (BZK), Ministry of Social Affairs and Employment (SZW) – be involved in the problems or consequences of an outbreak, then an inter-departmental committee for crisis management (ICCB) can be set up. The contributions made by the Ministry of Health, Welfare and Sport are substantively drawn up by the OMT and BAO after which the decision-making takes place in the ICCB. The departments are then individually responsible for the further dissemination of these recommendations.

3.6 Vaccination policy for the 2009 H1N1 virus

3.6.1 International

On April 29, 2009, the European Medicines Agency (EMEA) held a meeting with vaccine manufacturers. The European Commissioner for Health had a meeting with European vaccine manufacturers on the same day.

3.6.2 National

On April 29, 2009, the Minister of VWS placed an urgent request with the Health Council for advice on a number of issues concerning the use and the development and acquisition of vaccines for the 2009 H1N1 pandemic virus [F, April 29, 2009]. Below are the questions put to the Health Council:

1. Is there any expectation that the current seasonal flu vaccine will provide any protection, given the severe complications of infection with the 2009 H1N1 pandemic virus now circulating?
2. Can any protection that may be offered by the current seasonal flu vaccine be strengthened by the addition of a new generation adjuvant?

3. Would it be advisable – based on the current epidemiological state of affairs – to focus on developing and acquiring a vaccine that is based on the 2009 H1N1 pandemic virus?
4. What can be said regarding the possible protection and potential adverse reactions of the two options named above?
5. How do you weigh up the risks if an extra appeal were to be made on the production capacity regarding the production of seasonal flu vaccines for the coming flu season?
6. Are there any other considerations that you think we should know about.

Vaccination of the population during an impending pandemic is the most effective measure that can be taken [10, 11]. However, the production of a pandemic vaccine using standard methods takes approximately 4 to 6 months. This production period can, however, be shortened by taking such initiatives as the FLUSECURE-project (initiated by the European Union). Nonetheless, the chances of having a vaccine ready for use prior to the onset of a pandemic virus are limited. Because it is not known beforehand what the exact make up of the pandemic virus is, a standard vaccine that has been produced prior to the pandemic is likely to have little or no effect on the virus.

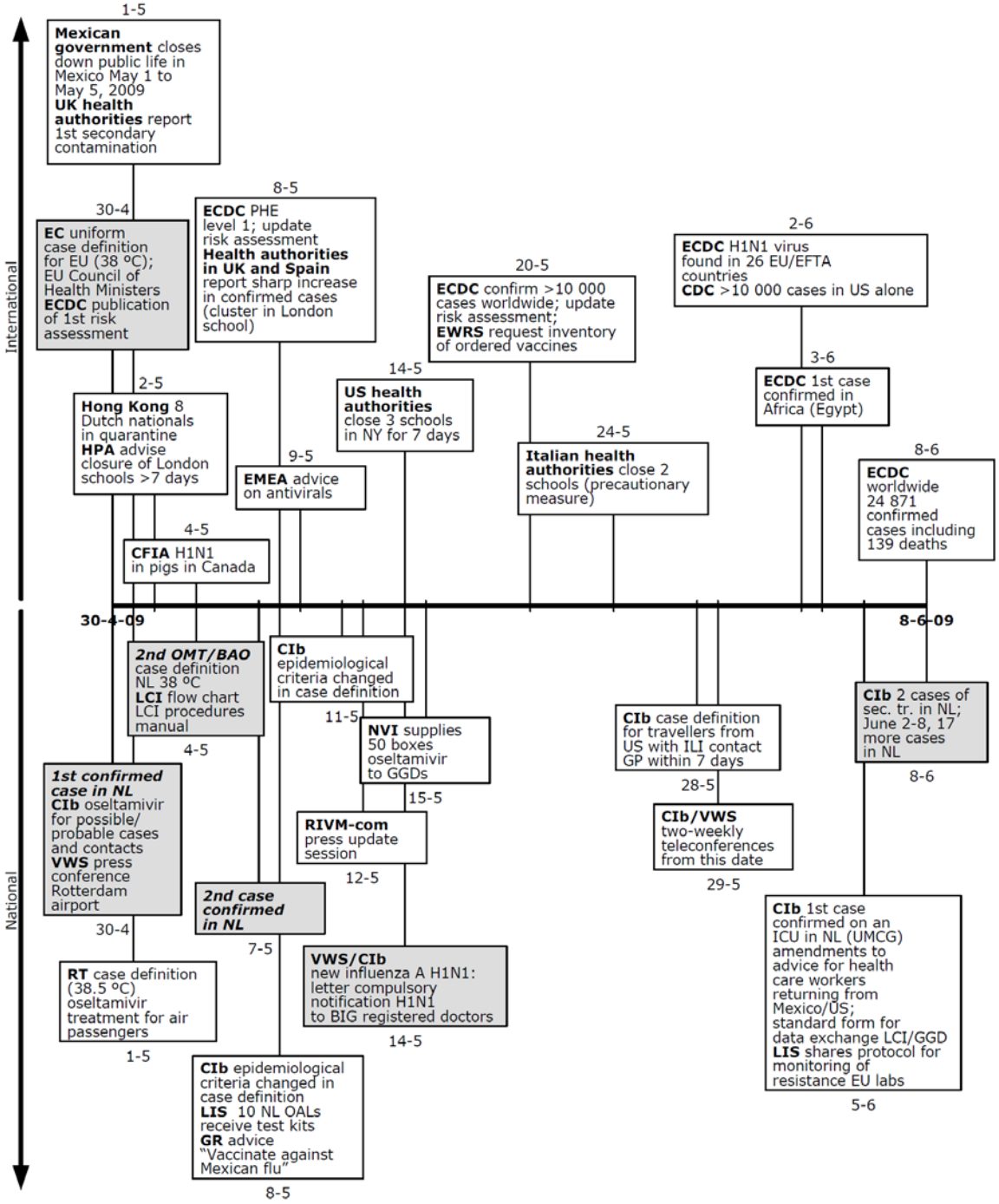

Figure 3 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period April 30, 2009 to June 8, 2009.

4 Period 2: from April 30, 2009 to June 8, 2009

The introduction of the new 2009 H1N1 pandemic virus into the Netherlands
On April 30, 2009, the CIb announced that the first cases of the 2009 H1N1 flu virus had been confirmed in patients in the Netherlands. This chapter describes what happened in the period during which the number of confirmed cases of 2009 H1N1 flu slowly increased in the Netherlands. In some European countries, such as Spain and the United Kingdom, the number of confirmed cases was increasing sharply. In this period, the regional Public Health Services (GGD) and the CIb were mainly occupied with tracing possible contacts and taking samples from travellers returning from Mexico and the US.

4.1 Situation

4.1.1 International

By April 30, 2009, the number of 2009 H1N1 flu cases confirmed through positive laboratory tests in Europe had slowly increased. On April 30, 2009, there was a total of 27 confirmed cases, located in 8 EU and EFTA countries. All these affected people had mild symptoms. Of these cases, there was 1 case in Spain where infection had occurred within the family, making it the first case of secondary transmission to occur in Europe. As far as the other cases were concerned, these were all travellers returning from Mexico [B, April 30, 2009]. On May 1, 2009, the first case of secondary transmission was reported in the UK [12].

On the same day, there were 454 confirmed cases outside Europe reported by the European Centre for Disease Prevention and Control (ECDC). It was thought that the primary reason for this sharp increase lay in a new series of laboratory results released by the Ministry of Public Health in Mexico. Up until then, Mexico had reported 312 confirmed cases and 12 deaths; the CDC had reported 109 cases in 11 different American states. In the US (New York) and Canada outbreaks were occurring in schools [B, May 1, 2009]. On May 5, 2009, the number of confirmed cases outside the EU had increased to 1162 cases [B, May 5, 2009].

On May 4, 2009, the Canadian Food and Consumer Product Safety Authority (CFIA) detected the presence of the 2009 H1N1 pandemic virus in a Canadian pig herd in Alberta [B, May 4, 2009]. It was thought that the virus had been transmitted from human to pig by someone who had travelled from Mexico and was now working in Canada on a pig farm [E, May 4, 2009].

On May 4, 2009, during a press briefing by the Mexican Secretary of Public Health, it was made known that cases had been confirmed in 26 of the 33 Mexican states. In Mexico 51.6% of the reported cases were under the age of 19 years and 17 of the people who had died (for whom age was known) were between the ages of 21 and 40 years [B, May 6, 2009]. Moreover, according to the WHO, it was young people in particular who were becoming infected with the 2009 H1N1 pandemic virus. The WHO then reported the following facts [B, May 6, 2009]:

- the proportion of confirmed cases was comparable in men and women;
- ongoing investigation showed that the incubation period of the new virus was between 1 and 7 days;
- infections in health care workers had been reported and investigations would be carried out as to whether or not these had been contracted whilst people were at work or in some other context.

During a WHO press conference on May 5, 2009, it was announced that after being isolated in different countries, the 2009 H1N1 virus had not yet shown any relevant mutation and was still sensitive to neuraminidase inhibitors.

On May 6, 2009, a woman in the US with underlying conditions died as a result of infection with the 2009 H1N1 pandemic virus; this was the second death to be recorded outside Mexico [B, May 7, 2009]. Up until this point, nobody in the EU had died as a result of the flu. However, the number of human to human infections in the EU was rising sharply although there was still no question of sustained human to human transmission [B, May 7, 2009].

In early May, the number of confirmed cases in Spain and the UK was increasing rapidly. Around May 8, 2009, there was a cluster of cases in the UK in a school in South West London [B, May 9, 2009]. This cluster led to a substantial increase in the total number of 2009 H1N1 flu cases in the UK [B, May 10, 2009]. The number of 2009 H1N1 cases was also increasing sharply outside the EU. On May 12, 2009, there were 5073 confirmed cases worldwide and 61 deaths (of which 56 in Mexico) due to the virus had been reported [B, May 12, 2009]. More and more countries worldwide were being confronted with cases of 2009 H1N1 pandemic flu, for example, China reported its first confirmed case on May 12, 2009. This case was a person in Chengdu who had travelled from the US [B, May 12, 2009; E, May 8, 2009].

In May 2009, the journal *Eurosurveillance* published several articles on the outbreak of the 2009 H1N1 virus [B, May 15, 2009]. Furthermore, the health authorities in Spain and the UK published articles on their first few confirmed cases. Spain reported that its first cases had all presented with only mild clinical symptoms and that the age of the confirmed cases corresponded with previous reports from Mexico and the US (14-55 years)[13]. As far as the ECDC was concerned, it remained unclear why people over 65 years of age were being less affected by the virus than those in younger age groups. This was a different situation to that of an outbreak of 'normal' seasonal influenza [B, May 24, 2009]. The ECDC thought that the possible reasons for this deviation were that the virus was circulating especially in children and young adults and had not yet reached the older age groups. An alternative theory was that younger people were more susceptible to an infection with the 2009 H1N1 flu virus because of its specific characteristics. Yet another possibility was that people in the older age groups had built up some immunity to this virus because they had previously been exposed to viruses that were similar to this one [B, May 14, 2009]. The UK reported in its article that 56% of all confirmed cases in the UK (N=65) had contracted the viral infection through secondary transmission – either within the family or through close contacts at school, et cetera. Just as in Spain, all affected people in the UK had mild symptoms which were similar to those of seasonal influenza [14].

By mid May 2009, the number of confirmed cases had further increased worldwide. Outside Europe, the number of cases was increasing sharply; this was particularly evident in the US (4714), Mexico (3103), and Canada (496) [B, May 18, 2009]. On May 16, 2009, it became clear that the virus was circulating not only through air traffic but also through international cruise ships. On May 16, 2009, a crew member on a cruise ship – that had completed a journey including Mexico, US, and Canada – was being examined for the 2009 H1N1 pandemic virus [B, May 16, 2009]. Furthermore, on May 27, 2009, the Australian authorities confirmed that 14 Australians had been infected with the virus following a trip on another cruise ship [B, May 27, 2009].

Following the weekend of May 16-17, 2009, there was a striking increase in the number of confirmed cases in Japan. Within a short space of time, the number of confirmed cases in Japan rose from 4 to 25. None of these new cases in Japan (who were all school children) had had any contact with the four previously confirmed cases in Japan or had made any recent trips abroad [B, May 18, 2009]. By May 24, 2009, the number of confirmed cases in Japan had increased to 338 [B, May 24, 2009]. The increase in the number of cases was primarily caused by outbreaks of the virus in schools. According to the Japanese authorities, there was still no indication that the virus would spread among the general population [B, May 20, 2009].

On May 18, 2009 the CDC reported on the 30 hospital admissions that were included in the 553 cases of 2009 H1N1 pandemic flu registered in California in the US. The median age of the patients admitted was 27.5 years, ranging from 27 days to 89 years; 19 patients (64%) had underlying conditions; 15 patients presented with pneumonia. Five of the 30 admitted patients were pregnant and 2 of these developed serious complications, although it was not clear to what extent these complications were due to the 2009 H1N1 flu virus. Half of all the admitted patients were treated with oseltamivir; 6 patients had been vaccinated for seasonal influenza [B, May 20, 2009].

In Europe an increasing number of cases was confirmed during May, particularly in Spain and in the United Kingdom [B, May 19; B, May 28, 2009]. The health authorities in Germany reported two unusual cases through the EWRS around May 16, 2009. After contact tracing of a previously confirmed case, two asymptomatic cases were found who had both received post-exposure prophylaxis [B, May 16, 2009]. On May 27, 2009, Greece reported two new confirmed cases of Greek nationals who may have become infected while they were in the United Kingdom. This was the first time that confirmed cases in Europe had also become infected in Europe. Prior to this, people who became infected were mainly travellers returning from Mexico or the US and/or the close contacts of such travellers [B, May 27, 2009; B, May 28, 2009]. According to the ECDC, there was no question of sustained transmission among the European population [B, June 8, 2009].

On June 3, 2009, the first case of 2009 H1N1 pandemic flu was reported in Africa; it occurred in Egypt [B, June 2, 2009]. In early June 2009, the ECDC reported a rapid increase in the number of confirmed cases in Australia. At the time, in those parts of Australia that were affected by the virus, the period in which seasonal influenza could be expected to break out was about to start [B, June 8, 2009]. On May 27, 2009 it became clear that the Australian state of Victoria was being hit hard by the 2009 H1N1 flu virus. The Australian health authorities were deploying antiviral agents on a large scale, both for possible and confirmed cases, in order to halt the rapid increase in the number of cases. For this reason, special flu clinics were being prepared to support hospitals in their task [B, May 27, 2009; B, June 8, 2009].

On June 8, 2009, there were a total of 24,871 cases of 2009 H1N1 flu confirmed worldwide which included 139 deaths from the disease [B, June 8, 2009].

4.1.2 National

On April 30, 2009, the CIb announced that the first case of 2009 H1N1 flu had been confirmed in a patient in the Netherlands. This patient was a 3-year-old child who had returned from Mexico on April 27, 2009 and who had developed fever and respiratory symptoms on the same evening [C, April 30, 2009]. The CIb reported that the child was doing well and that the child’s close contacts were being carefully monitored.

On May 7, 2009, the second case of 2009 H1N1 flu in the Netherlands was detected by the LIS and confirmed by EMC. This was a 53-year-old patient who had returned from a holiday in Mexico on April 30, 2009. The patient developed a cough on the plane during the journey home but only developed a fever on May 2, 2009 [E, May 7, 2009]. On May 8, 2009, the third case in the Netherlands was detected – again someone returning from Mexico [B, May 8, 2009]. The situation in the Netherlands regarding new laboratory-confirmed cases of 2009 H1N1 pandemic flu remained stable up to the end of May 2009 [E, June 2, 2009].

Up until June 5, 2009, the LCI had been consulted by the regional GGDs in respect of 146 patients and diagnostic testing had been performed for 72 of these people. Of these, 10 tested positive, 58 negative and the result was not yet known for the remaining 4 patients. Among the confirmed cases, 38 people were identified as being close contacts of an index patient although the diagnostic tests had not yet shown any cases of secondary transmission [C, June 5, 2009].

From June 2 to 8, 2009, the number of laboratory-confirmed cases in the Netherlands rose quickly, from 3 to 20 cases [B, June 2, 2009; B, June 8, 2009]. Moreover, the LCI reported that the first case of secondary transmission had occurred in the Netherlands around June 8, 2009 [C, June 8, 2009; E, June 8, 2009]. This related to a child and a colleague of two previously confirmed cases [C, June 8, 2009]. Up to this point, all confirmed cases in the Netherlands had presented with mild symptoms except for 1 patient who had to be admitted to an Intensive Care Unit [E, June 8, 2009]. This patient was admitted to the University Medical Centre in Groningen for symptoms that did not seem to correspond to those of the 2009 H1N1 flu. The patient had a viral pneumonia with a clinical condition that was described as extremely serious [C, June 12, 2009].

4.2 Diagnostics

4.2.1 International

On April 30, 2009, a uniform case definition was documented by the European Commission in Decision no. 2009/363/EC. This Decision was drawn up to establish the case definitions for reporting communicable diseases to the Community network [B, May 1, 2009]. The Decision was shared with the CIb through the EWRS. In this standard case definition, fever was determined as a temperature of 38 °C or higher [B, April 30, 2009].

In the United Kingdom on May 1, 2009, the Health Protection Agency (HPA) was the first authority in Europe to add the US (as well as Mexico) officially to the epidemiological criteria (visit to an area with sustained spread of the 2009 H1N1 pandemic flu virus in the population) to its case definition [E, May 1, 2009].

The laboratory capacity available in the EU Member States and EFTA countries increased more and more from May 2009 onwards. The WHO played a leading role in this respect. For example, the WHO organized the distribution of real-time PCR kits with primers and probes that had been specially designed for testing the 2009 H1N1 flu virus, to 23 national influenza centres in Europe. However, the PCR kit was found not to be ideal for its purpose.

As laboratory capacity began to increase, both in European countries and elsewhere, so the ECDC expected to see a large increase in the number of confirmed cases. This increase would not be the result of an increase in the actual number of 2009 H1N1 flu cases, but merely result from the countries' potential to retrospectively confirm

those cases that had previously been suspect cases and still required further examination [B, May 5, 2009; B, May 9, 2009]. For example, the ECDC reported on May 9, 2009 that in week 17 (2009), there had been an increase in the number of samples measured through the EU sentinel influenza surveillance system, but that the proportion of samples that tested positive for the new virus remained the same, i.e. about 6% [B, May 9, 2009].

4.2.2 National

On May 4, 2009, supported by the OMT recommendation, the case definition for a possible case of H1N1 flu was adjusted for the Netherlands by the CIb [G, May 4, 2009]. The criterion for fever of 38.5 °C was reduced to 38 °C [E, May 4, 2009]. On May 8, 2009, the CIb changed the epidemiological criteria of the case definition for a possible case. The indication for diagnostic testing was based on the clinical criteria (fever and respiratory complaints) combined with an epidemiological link as follows:

- a visit to an area with sustained spread of the 2009 H1N1 pandemic virus in the population (Mexico);
- direct contact with a patient infected with the 2009 H1N1 pandemic virus; or
- direct contact with animals where an infection with the 2009 H1N1 pandemic virus has been determined.

Point one of the epidemiological criteria of the case definition only applied to Mexico, but for patients who had returned from the US, it was also important to ask detailed questions about possible close contact with a known index case. This case definition therefore provided the necessary scope – based on an accurate risk assessment by the doctor involved – for also performing diagnostic tests on patients from or returning from the US [C, May 8, 2009].

On May 11, 2009, point 3 of the epidemiological criteria of the case definition (direct contact with animals) for a possible case, which had been communicated by the LCI on May 8, 2009 to professionals in the field, was removed. The reason for this was the evidence about the spread of the 2009 H1N1 flu virus as known at the time. However, the CIb included in the case definition the possibility of infection occurring in the laboratory environment [C, May 11, 2009]. In spite of the fact that sustained transmission was known to be taking place in 2 countries (Mexico and the US), the epidemiological criterion of 'an area with sustained spread of the 2009 H1N1 flu virus within the population' was only relevant to Mexico [B, May 10, 2009]. The scale of the spread in the US was less than that in Mexico which meant that the indication for further laboratory diagnostics did not apply to all travellers who developed fever (≥ 38 °C) and respiratory symptoms within 7 days of returning from a trip to the US. It only applied to people who had been in contact with a patient who had clinical symptoms of influenza. So, for daily practice this meant that the history of any presenting symptoms had to be taken carefully, for example, where had the patient been travelling and what had been the reason for that trip? How intensive had the contact been with the local population? Had there been any contact with people who were ill with the disease? If there were any doubts about the answers to these questions, people were advised to contact the LCI [C, May 20, 2009].

On May 28, 2009, the CIb added the US to the case definition after all. A clinical picture that fitted the pattern and a recent stay in the US (within 1 to 7 days of the first day of illness) were also indications for diagnostic testing [C, May 28, 2009]. All information and documents on the CIb flu website were modified accordingly – as were the posters at Schiphol airport [E, June 5, 2009].

In the Netherlands, in early May, the number of requests for diagnostic tests at the LIS and EMC increased sharply. To meet the increase in demand, the LIS analysts were repeatedly working at night to get through the analysis of the patient samples. On May 1, 2009, it became clear that the scaling up operation of the laboratories in the Netherlands was being delayed because of the distribution of the CDC protocols together with primers and probes that turned out to be less than ideal for the sensitive and specific diagnostic testing of the 2009 H1N1 flu virus [6].

This meant that the outbreak assistance laboratory (OAL) network (which included the two reference laboratories of LIS and EMC) were not properly prepared for the surge capacity. The Dutch NIC therefore decided to develop its own protocols, which were first distributed to the OAL network and were later made available to all microbiology laboratories; these protocols again included test panels for quality control [E, May 1, 2009].

Prior to this, the LIS and the EMC had estimated that they would be able to cope with a demand of 100 to 500 requests for influenza virus diagnostic tests over a period of just a few months [15]. However, in the response team meeting of May 4, 2009 it became clear that there was not enough laboratory staff at the LIS to cope with this demand. The perceived shortage was not necessarily due to the large number of test requests, but to the complex logistics and the classification of the virus to BSL-3 level. Classifying the virus in biosafety level 3 (BSL-3) meant that the range of actions with which virus growth is involved have to be performed in accordance with BSL-3 guidelines. In contrast, preparations for molecular diagnostics could be performed under BSL-2 conditions, in accordance with the WHO recommendations. In early May 2009, the LIS and EMC were still performing parallel tests on samples and conducting 2 rounds of diagnostic testing per day [E, May 4, 2009]. From May 6, 2009, the Laboratory for Zoonoses and Environmental Microbiology (LZO) offered assistance to the LIS [E, May 6, 2009]. Around May 8, 2009, the number of requests made to the LIS for diagnostic testing in travellers from regions other than Mexico increased [E, May 8, 2009].

Method used to detect the first case of the 2009 H1N1 pandemic influenza in the Netherlands:

- an Influenza A Matrix PCR;
- a PCR specific for N1 avian and pig sequences;
- a PCR specific for the 2009 H1N1 pandemic flu virus.

All tests proved positive. Other tests for human influenza (N1, N2, and N3) were negative. Specificity was confirmed by sequencing hemagglutinin and neuraminidase genes at the LIS and EMC [C, April 30, 2009].

On May 8, 2009 the RIVM found a mutation in the 2009 H1N1 pandemic virus taken from the second patient in the Netherlands. This mutation could have meant that the virus was changing into a variant that would be transmitted more easily in humans. This mutation was tested by EMC in animal and *in vitro* models. On the same day, the nine OALs in the Netherlands received kits containing the CDC primers and probes. This was the point at which the test phase for the scaling up operation began [E, May 8, 2009]. The test phase was intended for quality control of the diagnostic methods that were being used [6, 15].

This was done with the help of the External Quality Assessment (EQA) panels that were developed, distributed, and analyzed by the LIS and EMC in order to standardize the diagnostic quality in all of the OALs. Furthermore, after consultation

with the EMC it was agreed that the LIS would test the first 50 positive samples and every fifth negative sample from the OALs as a confirmation test; this would take place from the time the OALs became active until the comparison showed that the diagnostic tests were running well [6].

On May 11, 2009, the LIS reported through Labinf@ct that diagnostic rounds would take place once a day and that any diagnostic material that arrived before 11 am would be included in the round for that day. This meant that results would be available to the LCI at the end of the afternoon. Through Inf@ct, the regional GGDs were requested to make definite agreements with the LIS as to when the samples would arrive and when the results could be expected [C, May 11, 2009].

Resistance monitoring of antiviral agents: As part of its preparedness plan for an influenza pandemic, the Netherlands had acquired a national store of about 5 million courses of oseltamivir. If the 2009 H1N1 pandemic virus developed resistance to this antiviral agent, the consequences for public health would be serious [8]. For this reason, the RIVM clarified the resistance pattern of every virus through direct sequencing of clinical samples in order to determine the resistance to antiviral agents [E, May 15, 2009]. The phenotypic analysis of sensitivity could only be undertaken in BSL-3 conditions due to the classification of the new virus. The RIVM therefore developed a method to inactivate the virus with no loss of antigen and neuraminidase enzyme characteristics [16].

On May 19, 2009, the LIS advised the OALs (via Labinf@ct) to work with the Influenza A Matrix PCR (CDC kit). One laboratory did not want to use this kit but the LIS advised against any deviation [E, May 20, 2009]. On about May 25, 2009, the LIS and EMC reported that the OALs were able to correctly detect the 2009 H1N1 pandemic flu virus with the method used. Because of the less effective CDC primers, the LIS/EMC developed an in-house kit which, after a second quality control (EQA) was presented to the OAL network on June 17, 2009. This kit, which, if required, was later also available to other MMLs, could be used for the OAL diagnostic tests. On May 25, 2009, the LIS and the EMC were still able to perform all the diagnostic tests required in the Netherlands [E, May 25, 2009].

On May 19, 2009, permission was granted by the Medical Ethics Committee (METC) of UMC Utrecht for the supporting study on the 2009 H1N1 pandemic virus.

Set up of supporting study on the 2009 H1N1 pandemic virus In order to control a pandemic or potential pandemic as effectively as possible, procedures manuals have been drawn up and exercises have been held in recent years. In addition, the EPI also set up a study based on generic principles – translated as: *Influenza research during the phases of pandemic alert, December 2006*. This was intended to gain more insight into the course, risk factors and the effect of various interventions; in the event of the introduction of a new human influenza virus, this would be linked to the control measures for the first group of patients and their contacts. In February 2007, the METC at UMC Utrecht gave its approval to the EPI for setting up the generic research. The generic research was based on a new human influenza virus, from an avian or other source, and described the set up for the following studies:

- Wherever relevant (avian): research into people who have been exposed to animals infected with avian influenza, for example, incidental contact with birds or clearance staff at poultry farms.
- Patients with confirmed avian influenza infection in respect of whom information has been gathered by the treating physician and others.
- People who have been exposed to infected patients, for example, people working in the health care sector or members of the patient's household.

The generic proposal consisted of an integrated epidemiological, clinical, virological, immunological (humoral and cellular) and genetic research set up which considered the determinants, risk factors, interventions and the effectiveness of interventions. The generic proposal was examined by a collective research group from the CIb, Nivel, EMC, AMC, GGD Rotterdam and the Radboud University of Nijmegen in May, 2009. At this point, the focus was on the 2009 H1N1 pandemic situation and an amendment was subsequently sent to the UMC Utrecht's METC along with the following documents:

- information on the participants;
- consent forms;
- research protocol for contact investigation of the contacts of 2009 H1N1 pandemic flu patients;
- research protocol for studying cases of the 2009 H1N1 pandemic virus.

On May 19, 2009, permission for the research was received from the METC. The supporting research was financed by the Netherlands Organization for Health Research and Development (ZonMw). The supportive research on the 2009 H1N1 pandemic virus was started on June 29, 2009.

In July 2009, a follow-up amendment was submitted for a serum survey to be conducted before and after the pandemic in a random sample of the population; this was also approved by the METC. The serum study was conducted in September 2009 and April 2010.

On May 22, 2009, the LIS sent a message through Labinf@ct that together with the LIS and the EMC the OALs had tested an EQA panel that contained seasonal flu viruses and the 2009 H1N1 pandemic variant. The OALs were asked to repeat the test with the PCR kit that had been made available to them (based on the CDC protocols) as well as with their own diagnostic methods. The complete analysis of the results was still being rounded off, but the preliminary conclusions were:

- all of the OALs were able to detect the new flu virus specifically but there were
- differences in test performance due to differences in the implementation of the standard protocol;
- one of the PCRs from the CDC protocol showed cross-reactivity with seasonal influenza and was therefore less suitable;
- one of the PCRs from the CDC protocol was less sensitive than the LIS and the EMC would have liked.

Based on the evaluation, a protocol for an optimum method was made and validated [6].

Following the validation, a kit and a second quality control round (EQA) was prepared for the OALs and other laboratories together with a second round of quality control (sent on June 17, 2009) [E, May 22, 2009].

At the end of May, 2009, the LIS reported through Labinf@ct that various protocols were circulating in the OALs and that the results of the EQA panel were not optimal when using the CDC primers and probes [E, May 27, 2009]. Therefore, on June 5, 2009 the LIS announced that new protocols together with a new kit, EQA panel and positive control would be distributed among the OALs. These were delivered to the laboratories on June 17, 2009. In addition, the inactivation protocol for resistance monitoring was shared with European laboratories through the ECDC and the WHO-EURO networks [16].

At the beginning of June 2009, samples were no longer being tested for the whole range of respiratory pathogens but only for the 2009 H1N1 flu virus [E, June 5, 2009].

The External Quality Assessment (EQA) panels were developed, distributed and analyzed by the LIS and the EMC in order to standardize the diagnostic quality in all of the OALs. In addition, the EQA panels could be requested by other laboratories intending to perform molecular diagnostic tests for influenza, and by staff who wanted to check their own tests for accurate detection of the 2009 H1N1 pandemic virus. The EQA panel contained seasonal flu viruses as well as the 2009 H1N1 pandemic virus. The panel was accompanied by a document for reporting back on the results. As soon as this document had been received by the RIVM, the decoding of the panel was sent to the relevant laboratory. Laboratories could request a panel and/or the positive control [D, June 5, 2009]. This agreement was separate from the one whereby any clinical suspicion of infection with the 2009 H1N1 pandemic virus had to be discussed with the LCI for triage purposes (and sample material sent to the RIVM), but did allow the opportunity to verify in-house diagnostics [D, May 22, 2009].

On June 8, 2009, the LIS once more communicated that they could receive diagnostic material 24 hours a day – which had been the case since April 24, 2009 – providing the samples had been registered with the LIS beforehand through the front office of the RIVM (during office hours or between 11:00 and 17:00 at the weekends). Samples could be kept at room temperature. Furthermore, it remained essential for the regional GGDs to contact the LCI regarding the indication before continuing with the diagnostic tests. Some GGDs chose the option of taking samples from the patient's closest contacts at the same time as taking samples from the index patient, and sending these to the RIVM as well. These samples from the contacts were initially stored and only tested by the LIS and the EMC if the index case was confirmed as positive [C, June 8, 2009].

4.3 Control

4.3.1 International

By May 5, 2009, three of the six WHO regions had reported confirmed cases of infection. However, sustained transmission of the virus had only been reported by the CDC in the US [3]. At that point in time, there was no question of any sustained transmission in Europe [B, May 5, 2009]. However, the number of confirmed cases in EU and EFTA countries was increasing sharply. These were mainly people returning from Mexico and the US, although gradually there were more and more human to human transmissions occurring [B, May 4, 2009; B May 5, 2009]. According to the ECDC, the affected Member States had taken the correct containment measures (fast diagnostic testing, contact investigation, et cetera) needed to tackle the impact of the introduction and possible spread of the 2009 H1N1 pandemic virus in Europe [B, May 3, 2009; B, May 13, 2009]. However, the ECDC pointed out that where human to human transmission was concerned, it should be borne in mind that there could be some detection and reporting bias. This was because the surveillance in the EU Member States and EFTA countries was especially aimed at people who had a link with the affected areas (Mexico, US). The ECDC pointed out that this could lead to an underestimation of the number of human to human infections, and more especially to an underestimation of the number of transmissions within the population. This meant that continuous monitoring of the reported transmissions was crucial for selecting the correct measures to be taken, for example, containment versus mitigation measures. In the US, control shifted from containment to mitigation measures from early May, 2009 [B May 5, 2009].

Due to the increasing number of 2009 H1N1 flu cases, the Mexican government called for the closure of all non-essential public and private services in Mexico from May 1 to May 5, 2009. The Mexican population was asked to stay at home insofar as this was possible and all non-essential public services were suspended. However, transport and traffic facilities such as airports, harbours and bus stations did remain open.

On May 2, 2009 an entire hotel in Hong Kong (Metropark hotel) was placed under quarantine due to fears of the 2009 H1N1 pandemic virus spreading. At the time there were 200 guests in the hotel including 8 Dutch nationals and a number of other Europeans. These people were placed under a Quarantine Order after one of the guests was found to be suffering from the Mexican flu. Five Dutch nationals were admitted to hospital with mild fever. All of the hotel guests were given the antiviral prophylaxis of oseltamivir [B, May 3, 2009].

On about May 2, 2009, the Health Protection Agency (HPA) in the UK advised the closure of two schools in London for at least 7 days because of the outbreak of the 2009 H1N1 pandemic virus. The contacts of the school staff and pupils were offered antiviral prophylaxis [B, May 4, 2009].

The discovery of the 2009 H1N1 pandemic virus in a pig herd in Canada gave rise to worldwide unrest once more on May 4, 2009. Vets and pig farmers in Canada were asked by the Canadian Food Inspection Agency (CFIA) to increase biosecurity measures so as to protect the welfare of the animals. According to the WHO and the Food and Agriculture Organization (FAO) in the US, the consumption of pork was not harmful to human health [B, May 4, 2009].

On May 9, 2009, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) published two documents with their recommendations (below) on the use of antiviral agents for the treatment of patients during an officially declared pandemic of the 2009 H1N1 virus [B, May 9, 2009]:

- The benefits of using oseltamivir in children under 1 year of age outweigh the risks involved. A dose of 2-3 mg/kg body weight is recommended.
- Oseltamivir and zanamivir can be used safely to treat pregnant women and women who are breastfeeding.
- The oseltamivir capsules (Tamiflu®) that were already on the market can be used up to 2 years after the stated expiry date.

From mid May 2009, the ECDC introduced and distributed the so-called ‘passenger allocation cards’ to help countries record the contact investigation of airline passengers. Passengers were asked to fill out the card with their name, address and city of residence. This made it easier for national organizations in Europe to get in touch with airline passengers who may have been infected with the virus [E, May 15, 2009]. The policy concerning airline passenger contact investigation remained unchanged in Europe at this time – as decided during the EWRS/HCS teleconferences [E, May 20, 2009].

On May 24, 2009, 2 schools in Rome were closed by the Italian health authorities as a precautionary measure after 2 students (who had travelled to New York) tested positive for infection with the 2009 H1N1 pandemic virus. This resulted in the monitoring of 14 schools in Sicily by the Italian health authorities [B, May 24, 2009].

4.3.2 National

On April 30, 2009, the CIb announced through Inf@ct that the Ministry of VWS was planning to issue antiviral agents for any new patients and their contacts through the regular stores held by pharmacies in the Netherlands [C, April 30, 2009]. Should any problems arise during this operation, then antiviral agents would be issued by the NVI through the LCI in accordance with the procedures manual [8].

On May 1, 2009, again through Inf@ct, the LCI announced the response measures for tracing airline passenger contacts of 2009 H1N1 flu patients. Airline passengers who had been seated in the same row as the patient and those in the two rows in front and behind the patient (over the whole width of the plane) were traced. All these airline passengers were offered antiviral prophylaxis and were given an informative letter. This informative letter was compiled by the GGD of Kennemerland. The same measures applied to the cabin staff who had looked after these rows. The GGD of Kennemerland was given an overview of the airline passenger contacts by the airline, including their personal details, and then contacted the regional GGD where the contact lived. This local GGD was then responsible for any further measures that needed to be taken in respect of these contacts [C, May 1, 2009].

In May 2009, the number of aircraft passengers who proved to be contagious increased sharply. The CIb regularly received notices from colleagues abroad that Dutch passengers had been on board an aircraft that was carrying a contagious passenger. When these Dutch passengers were considered to be close contacts and therefore eligible for oseltamivir, the relevant GGD was alerted. The airlines usually sent all other passengers a letter containing general information. However, this occurred so frequently that the procedure requiring the LCI to contact all the regional GGDs of the passengers concerned quickly became too cumbersome. Should the GGDs receive any queries from passengers, they could always contact the LCI for the flight details and verify the policy implemented [C, May 28, 2009]. The contact tracing of airline passengers was very time consuming for both the LCI and the regional GGDs [E, May 14, 2009]. On June 8, 2009, the CIb decided to limit the contact investigation of airline passengers to just those people who had shown symptoms during the flight. This was decided because secondary transmission of the 2009 H1N1 pandemic virus among air passenger contacts had hardly ever occurred in advance of the onset of symptoms in the index case [C, June 8, 2009].

On May 4, 2009, the LCI sent a flow chart through Inf@ct 'Algorithm for the management of 2009 H1N1 pandemic influenza suspect patients' (see Appendix 2) to the regional GGDs; this flow chart showed a clear overview of the measures to be taken in suspected or confirmed cases [C, May 4, 2009]. The chart was based on the procedures manual: *Part 2: Incidental Introduction of a New Human Influenza Virus in the Netherlands* drawn up by the LCI [8].

By mid May 2009, it became clear that the control strategy pursued in the Netherlands – which was to perform source and contact investigation for each case in order to prevent the spread of the virus in the Netherlands – was justified in relation to the pandemic situation of the 2009 H1N1 flu virus in Europe and in the Netherlands. According to the ECDC, the disease was only breaking out in small clusters, with only sporadic local transmission. There was, therefore, no question of sustained transmission in the European community [C, May 14, 2009].

On May 15, 2009, the regional GGDs each received 50 boxes of Tamiflu® from the NVI in accordance with the distribution plan of the NVI and the LCI. Accompanying the delivery was a memorandum in which the NVI explained that although the boxes

were over the expiry date, the content had been retested again by the manufacturer. The boxes were therefore marked with a new expiry date. The GGDs had to keep note of the Tamiflu courses they had handed out and report this back to the LCI. New deliveries from the NVI could be arranged through the LCI. The oseltamivir that came from the national store was dispensed to affected patients free of charge [E, May 15, 2009].

Doses of oseltamivir for children had to be prepared by pharmacists in the Netherlands at the beginning of the outbreak of 2009 H1N1 pandemic flu from adult doses of oseltamivir (75 mg powder in a sachet) or Tamiflu® (75 mg per capsule) obtained from the NVI. As prescribed by the NVI, pharmacists diluted the correct dose from the adult dose of oseltamivir sachets or Tamiflu® capsules. Because this preparation method was not very practical due to the small amounts of powder needed, consultation with the Ministry of Health, Welfare and Sport led to doses for children being ordered from the manufacturer (Tamiflu® 30 mg and 45 mg). These children's doses of Tamiflu® were only available from November 2009 so that in the meantime, pharmacists had to prepare the dilutions themselves.

By May 20, 2009, more and more European countries were withdrawing their travel advice relating to Mexico because the illness itself seemed to be relatively mild and comparable to seasonal flu. Many countries therefore no longer considered it justified to advise against trips to Mexico. But the Netherlands Ministry of Foreign Affairs maintained a negative travel advice. Although the situation of sustained transmission of the 2009 H1N1 pandemic virus continued to exist in Mexico, the emphasis of advice to travellers to all regions where the virus was circulating was to take effective personal hygiene measures to prevent infection. The CIb theme site on flu and colds contained further information on such measures [C, May 20; C, May 28, 2009].

On May 20, 2009, the LCI announced through Inf@ct that the Turkish authorities had offered airline passengers on a flight from Amsterdam to Istanbul prophylactic oseltamivir because a Turkish passenger was found to have a confirmed case of infection with the 2009 H1N1 virus. On returning to the Netherlands, several people contacted their GGD to ask whether this measure had been necessary. Even though the Turkish policy differed from that of the Netherlands, the LCI advised people to finish the course of oseltamivir that they had started. However, pregnant women and women who were breastfeeding were advised by the LCI to stop taking the drug [C, May 20, 2009].

At the end of May 2009, as pressure began to build, the upscaling operation at the LCI began. There was evidence of extremely high workloads of LCI staff, both on-duty and stand-by duty – even outside office hours. Extra support wherever possible was provided by desk editors, communication department and secretarial staff.
In early June 2009, due to the increase in the case numbers, the data exchange between the GGD and the LCI for confirmed flu cases was standardized with the introduction of a special 'patient data' form. This form was in fact a check list for data that had to be systematically documented so that source and contact investigation could take place and for data on confirmed cases of 2009 H1N1 pandemic flu that the EPI had to pass on to the WHO. The regional GGDs were asked to use this form for each confirmed patient [C, June 5, 2009].

On June 5, 2009, the OMT's advice from May 4, 2009 concerning health care workers was changed by the CIb because the influenza virus was not yet showing any resistance to oseltamivir and the course of the disease was milder than had originally been expected. This adjustment meant that people working in the health care sector could resume their work after returning from a trip to an area with sustained

transmission (at that point, only Mexico and the US) as long as they were free of symptoms. This also applied if they had been in contact with severely immunocompromised patients, such as patients who were having chemotherapy, transplant patients or hemato-oncological patients. People working in the health care sector who had had contact with flu victims in the US or Mexico, or who had looked after patients in those areas, were still expected to stay away from any such immunocompromised patients for a period of 7 days after their return to the Netherlands [C, June 5, 2009].

At the beginning of June 2009, professionals working in the field alerted the CIb to the oseltamivir patient leaflet which indicated a 10-day prophylactic course of the drug instead of the 7 days recommended by the OMT on May 4, 2009. In spite of the fact that there was little evidence to back up extending the oseltamivir prophylaxis beyond 7 days, the CIb did decide to change its policy to a 10-day antiviral drug course in order to avoid any confusion. The procedures manual and the informational letters for flu contacts were changed accordingly [C, June 5, 2009].

On June 8, 2009, the CIb announced through Inf@ct that it was considering whether its former policy of 'active case finding' through contact investigation to prevent the further spread of the virus (containment phase) should not be replaced by one of mitigation. The mild course that the outbreak of the 2009 H1N1 flu was running did not seem to justify the range of control measures that were being recommended at the time. For this reason, preparations were made to simplify the rules for the protective measures required when taking material for diagnostics. However, any adjustments made to the policy in place called for the necessary liaison and consultation to reach agreement in the OMT and BAO meetings [C, June 8, 2009].

Containment phase: The policy phase in which the spread of the pathogen is controlled through applying such measures as source and contact investigation, prophylactic therapy, treatment and isolation of patients.

Mitigation phase: The phase in which the policy no longer focuses on limiting the spread of the pathogen but on limiting morbidity and mortality, for example, through appropriate hygiene measures and vaccination. Mitigation aims to reduce the impact of an epidemic as far as possible by the early detection and treatment of probable index cases without performing contact tracing and administering preventive prophylaxis to the contacts.

4.4 Government communications

4.4.1 International

On April 30, 2009, the ECDC announced their first risk assessment on the outbreak of the 2009 H1N1 pandemic virus. This was revised by the ECDC on May 8, 2009 and again on May 20, 2009. From the beginning of the 2009 H1N1 pandemic, the countries of the EU were asked by the ECDC and the European Commission to report their confirmed cases – in accordance with the European case definition – through the EWRS [8].

The LCI did this for the confirmed cases in the Netherlands by using the option '*report aggregated cases*' on the EWRS website. These reports were then integrated into the daily ECDC situation reports. However, this information contained little of the epidemiological data that is necessary for an optimum implementation of the instructions contained in the pandemic procedures manuals. For this reason, at the beginning of May 2009, the ECDC and the WHO liaised with the EU countries to start developing a system that could collate more detailed epidemiological data for each confirmed case in a systematic and coordinated manner. With such a system, the

international and national authorities would be able to gain better insight into the risk groups in the population and to make a better risk analysis for Europe [B, May 1, 2009]. This system came into use alongside the old system on May 5, 2009. The system enabled the EU and EFTA countries to add more case-related information to the EWRS using the option '*add individual case*' [B, May 5, 2009]. The LCI continued to report the aggregated cases and, from that date, the EPI supplemented the corresponding epidemiological data for each confirmed case in the Netherlands. Based on the data in Osiris provided by the regional GGDs, this was then linked to the laboratory data [E, May 1, 2009].

The WHO first paid attention to the 2009 H1N1 pandemic in its weekly epidemiological report (WER) from May 1, 2009. The objective of these reports was to share the epidemiological information on individual cases and outbreaks, as well as other relevant information through the WHO website [A, May 1, 2009; B, May 24, 2009]. The CDC also reported the epidemiological situation in the US through its MMWR weekly reports from the beginning of May, 2009 [May 20, 2009].

On May 1, 2009, the ECDC published the guideline for the measures that needed to be taken for 2009 H1N1 flu cases and their contacts on its website [17]. These measures were coordinated during teleconferences with the EU countries and the European Commission [B, May 1, 2009]. On May 4, 2009, the ECDC published a document on the measures to be taken for personal protection in order to reduce the risk of infection or the spread of the 2009 H1N1 pandemic virus. To this end, the ECDC published an information leaflet on how people could protect themselves against the new virus [B, May 4, 2009].

On May 5, 2009 the Standing Committee on the Food Chain and Animal Health of the European Commission gave a statement on the alleged human to pig transmission in a pig herd in Alberta, Canada. This statement mentioned that, based on the evidence available, there was no justification for banning the trade in pigs and pork products. Furthermore, it was mentioned that it was not yet completely clear what the exact role of pigs had been in the epidemiology of the outbreaks of the 2009 H1N1 pandemic virus and that further investigation was needed on this point [B, May 7, 2009].

From May 5, 2009, the ECDC organized a twice-weekly webcast (Tuesdays and Thursdays) in which the latest epidemiological developments and educational information on the 2009 H1N1 pandemic virus and its implications for public health were communicated with the national authorities in Europe [B, May 5, 2009].

Links from the ECDC to new publications on the 2009 H1N1 pandemic virus were regularly added to the ECDC situation reports under the heading 'publications of interest'. This was done from May 2009 onwards. This enabled users to gain quick and easy access to the most recently published articles on the 2009 H1N1 pandemic virus.

On May 7, 2009, the ECDC's webcast – broadcast through its website – discussed the transmission of the 2009 H1N1 pandemic virus in detail [B, May 8, 2009].

On May 15, 2009, information on the recommended precautionary measures advised for travellers was distributed through the ECDC website. This enabled national authorities to convey the information to travellers in their respective countries [B, May 15, 2009].

From the end of May, 2009, the most important media messages worldwide on the developments of the 2009 H1N1 pandemic virus were collected by the ECDC's Health Communication Unit and put in their daily strategic media monitoring briefs; please note that these documents were not complete summaries of events [B, May 27, 2009].

On June 2, 2009, the ECDC published a presentation with the title: *Likely evolution of the epidemics/pandemics of new A (H1N1) influenza*, on its website in which the scientific background of the 2009 H1N1 pandemic was set out. The presentation discussed various aspects of the last three pandemics of the twentieth century (1918, 1957, and 1968), including the age-specific clinical attack rate, mortality ratios and the epidemic curves. The ECDC presentation showed that there were significant differences between the type and duration of the earlier influenza pandemics, the risk groups, the severity of infections and the mortality ratios. The ECDC concluded in the presentation that control measures could not be standardized for all pandemics, but that these should reflect the up-to-date virological and epidemiological situation of a pandemic. The ECDC updated the presentation regularly by adding new insights that had been acquired on the 2009 H1N1 pandemic outbreak [B, June 2, 2009].

On June 6, 2009, the ECDC published a document (ECDC Interim guidance) on the policy to be pursued: containment phase versus mitigation phase which related to contact investigation [E, June 8, 2009]. The ECDC article discussed the essential background and presented evidence, experiences and practical considerations that could be used by the EU and EFTA countries to create a framework for their own policies. The ECDC indicated that it was important to give travellers clear instructions about what to do if they became ill on their return to Europe [B, June 6, 2009].

4.4.2 National

On April 30, 2009, the Ministry of VWS organized a press conference because the first case of 2009 H1N1 pandemic flu had been confirmed in the Netherlands. The Minister of VWS, the head of the CIb and Professor Ab Osterhaus, director of the NIC were present at this press conference. The press conference was held at Rotterdam The Hague Airport.

From April 30, 2009, the Minister of VWS opened the Postbus 51 public information helpline (0800-1351) to deal with telephone enquiries from the public at large [C, April 30, 2009]. On May 1, 2009, through Inf@ct, the LCI asked the regional GGDs to make arrangements to answer specific questions from the general public that Postbus 51 staff were unable to answer. A few examples of these arrangements were: to record messages onto tape, to open temporarily for dealing with questions from the public, and to answer questions via digital means [C, May 1, 2009]. Further, the GGDs were once more asked by the LCI (through Inf@ct) to make sure they could be reached if needed by professionals working in their region – especially on May 5, 2009 which was a public holiday in the Netherlands [C, May 4, 2009].

From early May 2009, the FAQs were updated on the CIb flu site on a daily basis and supplemented by RIVM-com.

During this period of early May 2009, prompted by the outbreak of 2009 H1N1 pandemic flu, the LCI received many requests (especially from doctors but also from other interested parties) for membership/access to the Inf@ct mailing list. The LCI responded by repeating (in an Inf@ct message) that the Inf@ct mailing list was not a 'news' medium as such but a closed and confidential method of communication for

the professional groups who were directly involved in the control of infectious diseases [C, May 11, 2009].

During the meeting of the response team on May 4, 2009, the LCI reported that some GGDs could not be reached by professionals and the general public during the weekend of May 2 and 3, 2009. This had happened in spite of the LCI's request through Inf@ct on April 29, 2009 to make themselves available. After consultation with GGD NL, the regional GGDs concerned were alerted to this fact by the LCI [E, May 4, 2009].

On May 4, 2009, a VWS and RIVM publicity campaign on the 2009 H1N1 pandemic was started in Dutch newspapers. In addition, RIVM-com started to send the leaflet 'flu pandemic' to hospitals and general practitioners [E, May 4, 2009].

On May 5, 2009, all the researchers at the EPI were given access to the CDC's epidemiological data. This meant that they were better able to follow the 2009 H1N1 pandemic situation in the US.

From May 6, 2009 onwards, the EPI and the LCI started the compulsory reporting to the WHO and the ECDC of the number of laboratory-confirmed cases of 2009 H1N1 pandemic flu in the Netherlands and later on also the deaths confirmed as H1N1 flu positive by laboratory diagnostics.

Compulsory reporting to the WHO and ECDC During the pandemic, reporting to the WHO and the ECDC was effected through various surveillance systems. On this point, differentiation must be made between the routine virological reporting systems and those relating to the pandemic.

Reporting of routine virological influenza and RSV
In a normal influenza season, virological influenza and RSV results are routinely reported by the LIS/EPI from week 40 through week 20 in the following year. Because of the 2009 pandemic, this surveillance was extended to cover the whole of that year.

Up to July 29, 2009, the European Influenza Surveillance Network (EISN) was used for the routine surveillance of influenza. On June 30, 2009, TESSy – for reporting to the ECDC – also became operational. From this date, the EISN system continued to be used for reporting to the WHO. This meant that from June 30, 2009 onwards, double reporting was necessary to provide both the ECDC and the WHO with data.

On July 29, 2009, EISN was officially taken over by EuroFlu, although in reality this transition took a few weeks to complete due to a few practical problems. From July 2009, both the EuroFlu (WHO) and TESSy (ECDC) systems were used to report the weekly virological results of influenza and RSV that were forthcoming from the sentinel and non-sentinel influenza surveillance systems in the Netherlands.

The following data items were reported to TESSy and EISN/EuroFlu every week:
- the total number of patients tested;
- the number of positive patients per influenza type and subtype;
- the total number of patients positive for RSV;
- the total number of patients tested for the 2009 H1N1 pandemic virus.

If viruses resistant to oseltamivir were detected, this information would be added to the upload by means of a comment. This would then appear in the weekly update.

Reports related to the pandemic

From May 6, 2009, the CIb started to report the number of confirmed cases of 2009 H1N1 pandemic flu to the EWRS – later on, this included deaths confirmed as H1N1 positive by laboratory testing. From May 14, 2009, the LCI/EPI reports to the EWRS were case-based. This data included the core details of patients, as derived from the special 'patient data' form and from the GGD's Osiris system. As the number of cases in Europe increased, so did the need for more aggregated reports so that reporting to the EWRS was discontinued after a few weeks.

Weekly reports to the WHO

The WHO received weekly reports from the EPI containing aggregated data. Up to July 29, 2009, these reports were sent to the EISN and after this date to EuroFlu. This information was derived from the patient data form and from Osiris.

Aggregated data to the WHO

- Cumulative number of laboratory-confirmed cases: from May 6, 2009 to August 15, 2009 (time of change to case definition due to amendment of notification obligation).
- Cumulative number of hospital admissions for laboratory-confirmed influenza per week: from May 6, 2009 to January 18, 2010. Weekly report of the cumulative number of deaths resulting from laboratory-confirmed influenza, subdivided according to age group.
- Cumulative number of ICU hospital admissions for laboratory-confirmed influenza per week: from September 23, 2009 to January 18, 2010. Weekly reports of the number of cumulative hospital admissions and ICU admissions, subdivided according to age group.
- Severe Acute Respiratory Infection (SARI) with details of the category: from June 1, 2009 to October 6, 2009. Weekly reports of the number of SARI cases and SARI deaths, subdivided according to age group. The Dutch SARI case definition (admitted to hospital for an infection with 2009 H1N1 pandemic flu and pneumonia as a complication) did not completely concur with the SARI case definition used by the WHO and the ECDC. For this reason, no further reports of SARI cases were made to EuroFlu after October 6, 2009.

Weekly reports to the ECDC

The ECDC received weekly aggregated and individual data from the EPI. This was done to EISN up to June 30, 2009, and after this date to TESSy.

Aggregated data to the ECDC

- Cumulative number of laboratory-confirmed cases: from May 6, 2009 to August 15, 2009 (time of change to case definition due to amendment of notification obligation).
- Cumulative number of hospital admissions for laboratory-confirmed influenza and deaths per week: started on September 7, 2009 and continuing through 2010. Weekly aggregated numbers for hospital admissions and deaths (cumulative per week) subdivided according to age group.

Individual data to the ECDC

- SARIs with data on the category: started on September 7, 2009 and continuing through 2010. This upload contained individual data on the SARI cases in respect of demographics (age, sex), date of onset of symptoms, date of hospital admission, notification date, treatment, prophylaxis, underlying complaints, ICU admission, ventilation and yes/no mortality.

Solution for double reporting in EuroFlu (WHO) and TESSy (ECDC)

On October 7, 2009, the CIb was informed that the WHO and the ECDC were working on a solution for the problems associated with double reporting in EuroFlu and TESSy. This solution was only implemented on January 18, 2010. From this date onwards, reporting to TESSy alone was sufficient; data was forwarded automatically to EuroFlu. This did not apply, however, to data on the SARI cases which was only reported to the ECDC.

Representation of the data collection by the WHO and the ECDC
The reports to the WHO and the ECDC can be found through the following sources:
- WHO/Europe Influenza Surveillance (www.euroflu.org);
- ECDC Weekly Influenza Surveillance Overview (WISO);
- European Influenza Surveillance Network (EISN) (http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx).

On May 8, 2009, the LCI placed two sample letters – the 'intensive contact letter' and the 'patient information letter' – on the CIb theme website. The GGDs could use these letters to inform patients and their contacts about the use of oseltamivir, hygiene and any other measures that needed to be taken. The sample letters were drawn up by the regional GGD in Utrecht. Because there were many questions on how to respond to suspected cases of 2009 H1N1 pandemic flu from professionals working in the field, the LCI sent a standard letter through Inf@ct on May 8, 2009 that could be used by the GGDs to bring professionals in their region up-to-date [C, May 8, 2009]. In addition to this, the LCI regularly used Inf@ct messages to repeat the instructions for application of the case definition, indications for diagnostic testing and any necessary control measures [C, May 7, 2009; C, May 8, 2009].

On May 12, 2009, RIVM-com organized its first press update meeting which was held at the RIVM premises; the purpose of this meeting was to provide the press with more detailed information on the 2009 H1N1 pandemic. The meeting was well attended by about 25 journalists. The presentations given by the experts at this meeting was placed on the CIb's flu website. The presentations could be used as background information by GGD professionals when preparing informational activities for the general public. [B, 14 May 2009].

On May 14, 2009, after consultation with the Ministry of VWS and the CIb, the nomenclature for the new virus was changed by RIVM-com. In order to stay in line with other European countries, it was decided to change the name 'Mexican flu' into 'novel influenza A (H1N1)'. The Netherlands was in fact the only country using the name Mexican flu [C, May 14, 2009]. That prompted the Mexican ambassador in the Netherlands to complain about this usage [E, May 8, 2009]. The nomenclature was therefore changed in all relevant documents and on the home pages of the RIVM and the CIb. On the CIb flu website that contained all relevant information, the virus was referred to from that date as the 2009 H1N1 pandemic virus [C, May 14, 2009].

Because it remained fairly quiet as far as questions from the public were concerned, the Postbus 51 public information helpline was closed in the weekend of 16 -17 May, 2009 [C, May 14, 2009].

At the beginning of June 2009, in addition to the updates that GPs received from the GGDs, they were also asked by the LCI – via the Dutch College of General Practitioners (NHG) website – to keep them up-to-date with the latest developments on the case definition (e.g. enlargement of areas with transmission) [C, June 2, 2009].

On June 2, 2009, the Dutch television programme 'EenVandaag' filmed a meeting of the response team. These shots were used for a documentary on the control of the 2009 H1N1 flu outbreak in the Netherlands [E, June 2, 2009].

From June 4 onwards, any new cases of 2009 H1N1 flu were reported through the CIb's website and not through Inf@ct. The overview on the pandemic on the CIb

website was updated daily by the EPI. At this point, the CIb expected the number of requests for diagnostic tests to increase sharply – which was also likely to lead to an increase in the number of confirmed patients. This trend was taking place throughout Europe [C, June 4, 2009].

On June 4, 2009, the special Postbus 51 public information helpline for influenza queries was closed down. Members of the public could hereafter place enquiries through the regular information number of Postbus 51, (0800-8051) or through www.postbus51.nl. All queries on the 2009 H1N1 pandemic were then answered from this number. This was a free telephone helpline that was open on weekdays from 08:00 to 20:00.

Around June 5, 2009, the procedures manual *Incidental Introduction of a New Human Influenza Virus in the Netherlands* was revised [8]. The changes included revisions to internet links and to nomenclature as well as the addition of the algorithm for patient management and the updated policy for oseltamivir [C, June 5, 2009].

4.5 Meetings

4.5.1 International

On April 30, 2009, a conference was held in Brussels for all the EU Ministers of Health. During this conference, the current situation and the policy on the 2009 H1N1 pandemic was discussed. One of the things that was reported related to the far from balanced distribution of vaccines for the rest of the world (outside Europe); the ECDC made it known that they would not be playing a leading role in the stockpiling and distribution of vaccine stocks [F, May 1, 2009].

On May 4, 2009, the CDC held a press conference in which they presented their first epidemiological findings on the confirmed cases (N=226) in the US up to that date [B, May 5, 2009]:

- the median age of confirmed cases was 16 years;
- 62% of the confirmed cases in the US were younger than 18 years;
- at that moment there were 35 people admitted to hospital, one patient had died.

On May 12, 2009, a teleconference was organized by DG-SANCO via the EWRS which was intended for vaccine experts in Europe; they were to discuss the production and distribution of the 2009 H1N1 pandemic flu vaccine. The LCI and the NVI took part in this conference on behalf of the RIVM. During the conference, the latest developments regarding the development and production of the 2009 H1N1 pandemic flu vaccine were shared with the EU and EFTA countries [E, May 14, 2009].

From 18 to 22 May, 2009, the 62nd session of the World Health Assembly (WHA) was held in Geneva. In this session several aspects of public health were discussed, including the necessary preparations for an influenza pandemic such as the sharing of vaccines and the accessibility of vaccines [B, May 18, 2009].

On May 19, 2009, there was a meeting between the heads of the WHO and the United Nations with more than 30 vaccine manufacturers. This meeting was organized to ensure that the vaccines for the 2009 H1N1 virus would be made available to everyone, which included developing countries, in an honest and fair manner [B, May 20, 2009].

4.5.2 National

In the Netherlands, the OMT met for the second time on May 4, 2009. At this meeting, the OMT made the following recommendations:

- The length of prophylactic treatment with oseltamivir for contacts was set at 7 days. This was irrespective of how long after the index patient the contact was traced.
- Patients treated with oseltamivir were, as a precautionary measure, advised to avoid social contacts for 10 days after the onset of disease symptoms, and only then if they had shown signs of clinical recovery. The OMT's decision on this point was based on data relating to the secretion of the virus in symptomatic patients during an epidemic of seasonal influenza. In most patients the secretion of virus particles lasts for 7 days after the onset of disease symptoms; in a small number of patients, it can last a few days longer.
- The OMT recommended amending the case definition and thus the diagnostic criteria for people returning from Mexico and for the contacts of confirmed patients. The fever criterion was lowered to 38 ºC in line with the EU's case definition.
- Health care workers who had been on holiday in Mexico and those who were involved in caring for severely immunocompromised patients – such as bone marrow transplantation patients – were advised to contact their occupational physician for further advice, and to avoid contact with these patients for a period of 7 days. Further consultation took place between the representatives of the Dutch Working Party on Infection Prevention (WIP) in order to define this category of immunocompromised patients more clearly.

The above recommendations were accepted by the BAO on May 4, 2009 and the Minister of VWS issued a decision on that basis [H, May 4, 2009].

On May 4, 2009, there was also a meeting between the Animal Health Service (GD) and pig farmers to give information to the farmers about the 2009 H1N1 outbreak in a pig herd in Canada. The possible human to animal transmission was also discussed in the meetings of the OMT and the response team which were held on the same day and questions were added to the FAQ list on the RIVM's website; this information had first been streamlined with the Ministries of LNV and VWS. According to the response team, surveillance of the virus in pigs in the Netherlands was not necessary in the Netherlands [E, May 4, 2009].

The Health Council of the Netherlands met on May 7, 2009 to formulate recommendations regarding vaccination against the 2009 H1N1 virus following an urgent request from the Ministry of VWS on April 29, 2009. This advice was published in the letter of recommendation: 'Vaccination against Mexican flu' [I, May 8, 2009].

4.6 Vaccination policy for the 2009 H1N1 virus

4.6.1 International

On May 20, 2009, the EU countries were asked by the ECDC through the EWRS to make an inventory of the vaccines on order and to indicate their margins for sharing with other countries should this prove necessary. The inventory for the Netherlands was carried out by the Ministry of VWS [E, May 20, 2009].

On June 3, 2009, in its situation report the ECDC reported on a number of vaccine issues that the international health authorities (WHO, ECDC, CDC, EMEA and FDA) were considering in relation to the development and production of a vaccine for the 2009 H1N1 pandemic virus [B, June 3, 2009]:

- Vaccine seed strains: During the production process of a vaccine, various techniques can be used. In the case in question here, at the basis of all these techniques was the isolation of the wild type virus from an infected individual from California. This wild type virus was in the meantime being distributed by the WHO to vaccine manufacturers in May 2009. At the end of May 2009, the WHO Collaborating Centres distributed the vaccine seed strains that had been produced using reversed genetic or reassortment techniques. The WHO estimated that most of the vaccine manufacturers would choose seed strains for the vaccine from those that had been produced through reassortment techniques. This is because reassorted strains carried the recommended hemagglutinin and neuraminidase antigens on the outside of a rapidly growing influenza virus strain in the laboratory. These reassorted strains could grow on a protein or cell-based culture, depending on the preference of the vaccine manufacturer.
- Adjuvants: Some vaccine manufacturers looked at the possibility of using a new adjuvant. Adjuvants are components that are added to a vaccine in order to increase the level of immunogenicity of the vaccine. For example, aluminium hydroxide was used as an adjuvant for decades. Nowadays, new components that use oil-in-water emulsions have been found to be more effective at stimulating the immune system. Using an adjuvant can have an antigen-sparing effect and trigger a broader immune response to discrete although related influenza variants. During that time there were already various approved vaccines on the European market; the assembled knowledge could be used to further develop a vaccine that would be effective against the 2009 H1N1 flu virus.
- Clinical trials: Before it can be registered, each new vaccine must be tested in clinical trials. The ECDC reported that vaccine manufacturers were planning to conduct clinical trials at the beginning of June 2009, providing the first vaccines were ready. During these trials, the immunogenicity and safety of the vaccine would be evaluated in young children, teenagers, adults and older people.
- Vaccine safety: The safety of a vaccine is always monitored during the initial phases of the clinical trials, as vaccine safety is itself part of a clinical trial. Regarding the uncommon side effects, all vaccine manufacturers are obliged, in accordance with the EMEA's risk management points, to clearly indicate how they will uphold the safety and effectiveness of the vaccine in the general population during the post-authorization phase. The ECDC indicated that the level of monitoring of side effects in pregnant women should be raised.
- Vaccine availability: The availability of a vaccine depends on several factors that all take time to complete, such as its production, the clinical trials and the procedure for its authorization.

4.6.2 National

In the letter of recommendation from the Health Council of the Netherlands dated May 8, 2009 'Vaccination against Mexican flu', it was concluded that the then available flu vaccine against seasonal influenza would not offer protection against the 2009 H1N1 virus. This in turn led to the conclusion that even if other adjuvants were added to the vaccine, it was still unlikely that it would then offer effective protection against the H1N1 flu virus. The Health Council offered two policy options in its letter of recommendation concerning the acquisition of vaccines, and included a risk assessment for both options. These two policy options were as follows:

- to adopt a wait-and-see policy and not order any vaccines;
- to set up an active vaccine policy and order vaccines based on the 2009 H1N1 pandemic virus.

The Health Council advised, should the government decide to purchase vaccines, that an adjuvanted vaccine based on the 2009 H1N1 flu virus would be the preferred option, provided its safety and effectiveness had been very carefully checked. The Health Council expected that it was unlikely that ordering the new vaccine would adversely affect the production capacity of the vaccine for seasonal influenza. Further stated in the letter of recommendation was that the ordering and the usage of vaccines should be seen as separate parts of the procedure. In the case of a mass vaccination policy being decided – and the occurrence of an unexpected situation of insufficient vaccines being available for the entire population – the Health Council advised first vaccinating people in the medical risk groups as defined in its interim report 'Antiviral agents in an influenza pandemic: application in times of shortage' (05/2004). In accordance with the advice, translated as: 'Influenza vaccination: revision of the diagnostic indication' (09/2007), the Health Council deemed it advisable to recommend vaccination for all health care workers who had direct contact with patients [I, May 8, 2009].

In order to back up the decision-making process with statistics, on June 5, 2009, the memorandum, translated as: 'Model-based analysis of vaccination against the 2009 H1N1 virus in a pandemic in the Netherlands' was drawn up by the EPI and sent to the Ministry of VWS. The memorandum contained a model calculation for scenarios in which the 2009 H1N1 pandemic vaccine would be delivered from October 31, 2009 onwards.

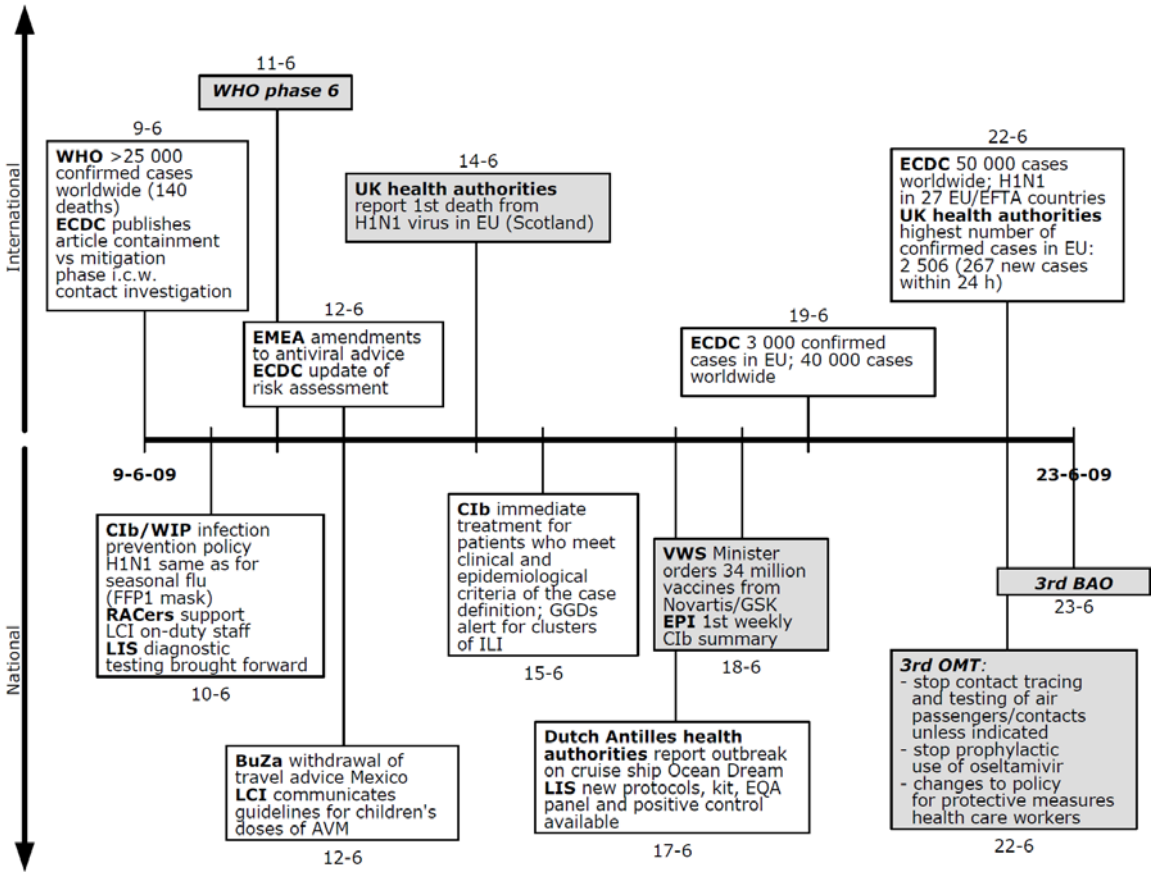

Figure 4 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period June 9, 2009 to June 23, 2009.

5 Period 3: from June 9, 2009 to June 23, 2009

Limited spread of the 2009 H1N1 pandemic influenza virus in the Netherlands

On June 11, 2009, the WHO declared that the outbreak of the 2009 H1N1 flu virus had turned into a pandemic. The first death of a patient infected with the 2009 H1N1 virus in Europe was recorded in the United Kingdom on June 14, 2009. In the Netherlands, the number of laboratory-confirmed cases of 2009 H1N1 flu increased gradually during June 2009. Moreover, there was evidence of a limited spread of the new virus in patients in the Netherlands. On June 18, 2009, the Ministry of VWS announced that it had ordered 34 million doses of the H1N1 vaccine in order to vaccinate the population. Towards the end of period 3 of the pandemic, the control measures were amended to accommodate the OMT recommendations; this included no longer tracing the contacts of infected patients and no longer prescribing antiviral agents for prophylactic treatment. These measures brought the containment phase in the Netherlands to an end.

5.1 Situation

5.1.1 International

In June 2009, both the number of confirmed cases worldwide and the number of secondary transmissions in the various countries were steadily increasing. On June 9, 2009, the WHO reported that more than 25,000 cases of 2009 H1N1 flu had been confirmed worldwide, and that 140 deaths had occurred [A, June 9, 2009]. On June 10, 2009, the ECDC reported that the country of Chile had the highest number of new confirmed cases of 2009 H1N1 flu (804) worldwide. One day earlier, the health authorities in Brazil had made it known through the H1N1 EPI bulletin (June 9, 2009) that 30 of their 40 new confirmed cases had become infected outside their home country. Two confirmed cases were travellers who had come from Europe [B, June 10, 2009]. The health authorities in Greece reported to the ECDC that a third person who had travelled from the UK had been confirmed as infected – once more a transmission within Europe.

On June 11, 2009, the Director General (DG) of the WHO raised the level of pandemic alert from phase 5 to phase 6. This decision was taken following the fourth meeting of the WHO Emergency Committee. The Commission had looked closely at the available information on the transmission of the 2009 H1N1 flu virus in some countries in a number of WHO regions and had reached the conclusion that the criteria for an official pandemic (phase 6) had been met [A, June 11, 2009]. The WHO criteria of pandemic alert phase 6 state that there must be proof of sustained transmission within the population in at least 2 WHO regions. These criteria are not, however, based on the severity of the disease that is caused by the virus itself [B, June 11, 2009]. As part of the statement given by the WHO, further explanation on this point indicated that the 2009 H1N1 pandemic virus could be described as moderately severe with mild symptoms [A, June 11, 2009; C, June 11, 2009].

In reaction to the increased level of the WHO pandemic alert, the ECDC stated that raising the alert level would not automatically result in any changes being made to the then-prevailing ECDC risk assessment for EU and EFTA countries. According to the ECDC, there were still some unresolved issues relating to the severity of the disease, the specific risk groups and whether or not the virus would remain sensitive to the antiviral agents that were available. Moreover, any co-circulation of other types of the new virus could result in genetic recombination of the existing seasonal

influenza virus and the avian H5N1 virus [B, June 11, 2009]. Prior to the emergence of the 2009 H1N1 influenza virus, avian influenza A (H5N1) was endemic in poultry and cases had occurred in humans in Egypt and Vietnam. These two countries had also been affected by the 2009 H1N1 pandemic virus. At the beginning of June 2009, there were confirmed cases of infections with the H5N1 followed by the H1N1 virus in these countries; this increased the risk of recombination occurring between the two variants [B, June 18, 2009].

In early June 2009, the ECDC expected that all EU and EFTA countries would ultimately be confronted with the new virus. The biggest changes for European countries were expected to occur when sustained virus transmission took place within the populations of these countries. On June 11, 2009, the virus had been reported present in 26 of the 30 EU and EFTA countries; up to this date, sustained transmission in humans had only been reported through the EWRS in the UK [B, June 11, 2009].

On June 14, 2009, the ECDC reported the first death in Europe as a result of the 2009 H1N1 pandemic virus; this occurred in Glasgow, Scotland. The case was a 38-year-old woman with underlying conditions who was being treated in hospital [B, June 15, 2009]. On June 15, 2009, the CDC reported that, just as with an outbreak of seasonal flu, many children under the age of 2 years had been admitted to hospital with flu symptoms. However, in contrast with a seasonal flu situation, older people were now underrepresented as far as the cases of 2009 H1N1 influenza were concerned. In its MMWR report, the CDC addressed the risk factors for hospital admission and for severe cases of infection. According to the CDC, the risk factors were chronic conditions such as asthma or chronic obstructive pulmonary disease and other conditions that caused respiratory insufficiency. Around June 15, 2009, the CDC stated that the mortality surveillance system had not registered any striking increase in mortality due to pneumonia or influenza [B, June 15, 2009].

On June 17, 2009, the health authorities in the Dutch Antilles reported the first transmission of the 2009 H1N1 flu virus. An outbreak of the H1N1 virus had occurred on the ship Ocean Dream and the ship had been placed under quarantine [E, June 17, 2009; B, June 19, 2009]. The Dutch Antilles and Aruba reported their WHO notifications of newly-confirmed cases of influenza to the Pan American Health Organization (PAHO) which subsequently sent a copy to the CIb [E, June 22, 2009].

On June 18, 2009, the ECDC communicated in its situation report that the first case of 2009 H1N1 flu in Sub-Saharan Africa had been reported. This was a traveller returning from a trip to North America. A further report in the international media on June 18, 2009 was that of an outbreak of the 2009 H1N1 flu virus on a cruise ship in the Caribbean islands. The cruise ship, carrying more than 1200 passengers on board, was placed under quarantine. After three infected cases had been confirmed, all the ship’s passengers and crew had been prevented from going ashore at stops made in Barbados and Grenada. According to the SHIPSAN project, this was the fifth cluster to occur on a cruise ship since the onset of the pandemic. The first outbreak on a cruise ship had occurred on May 25, 2009 [B, June 18, 2009].

On June 22, 2009, the ECDC reported that 50,000 cases of 2009 H1N1 influenza had been confirmed worldwide. At the time, 27 EU and EFTA countries were dealing with the new virus, with the United Kingdom having the most confirmed cases. In the space of just one day, 267 new cases of confirmed infection were reported in the UK [B, June 22, 2009]. In the US, the first cases of 2009 H1N1 virus infection reported by the CDC had occurred among health care workers [B, June 23, 2009].

5.1.2 National

On June 10, 2009, the CIb reported that 30 cases of infection with the 2009 H1N1 virus in the Netherlands had been laboratory-confirmed. Of these 30 cases, 6 had contracted the infection in the Netherlands and they were all contacts of patients who had previously been confirmed as infected [C, June 10, 2009]. On June 12, 2009, the CIb announced that there were 43 cases of 2009 H1N1 flu infection in the Netherlands, 29 of which were index cases and 14 contacts [C, June 12, 2009].

On June 15, 2009, in a message sent through Inf@ct, the LCI warned the regional GGDs to stay alert for clusters of influenza-like illness in the Dutch population. Up until that point in time, 61 people in the Netherlands had been confirmed as infected with the 2009 H1N1 virus. Of these patients, 33 had contracted the infection abroad and 28 in the Netherlands. The CIb reported that the proportion of infections transmitted in the Netherlands was increasing sharply. At that time, cases had been detected that were fourth generation cases of infection – contact of a contact of a contact of the index patient – which represented the first cluster of the 2009 H1N1 flu virus in the Netherlands [C, June 15, 2009]. Some of the clusters that had occurred in the Netherlands were described by GGD consultants for communicable disease control in the *Infectieziektebulletin* volume 20, no. 7 (2009) [18-20]. This meant that the spread of the virus in the Netherlands was no longer limited to people who had been in Mexico or the US and their direct contacts. Yet, although this was the situation, no warnings of infections with the 2009 H1N1 virus had come from the regular CMR surveillance monitoring stations run by the NIVEL. The incidence of influenza-like illness reported by the CMR monitoring stations remained low, well under the baseline measurement – 5.1 patients with influenza-like illness per 10,000 people – which was normally used to measure emerging epidemics. Equally surprising was the absence of the 2009 H1N1 influenza virus in the samples investigated. The EPI calculated that every patient who tested positive for influenza-like illness at the monitoring stations represented approximately 4031 symptomatic infections in the population. The regional GGDs were advised by the LCI to be particularly alert to unusually high numbers of school pupils with fever (> 38 °C) and a respiratory infection [C, June 15, 2009].

Sentinel network / CMR monitoring stations for influenza-like illness and influenza virus in the Netherlands: The CMR surveillance monitoring for influenza-like illness (sentinel data) takes place at the CMR monitoring stations in collaboration with the NIVEL and the NIC (RIVM/EMC). The CMR monitoring stations were set up in 1970. The stations cover approximately 0.8% of the population in the Netherlands and are intended to be as representative as possible for the entire population with regard to age, sex, region and level of urbanity. Each year, the extent to which this representation has been realized, is described in the CMR's annual report on the NIVEL's 'Continuous Morbidity Registration Monitoring Stations'. At the end of June 2009, because of the influenza pandemic, it was decided to expand the influenza surveillance of the monitoring stations for a 1-year period by admitting 12 general practices that were affiliated to the National Information Network for General Practice (LINH). The LINH network is a close-knit network of general practices that could offer more additional surveillance options and make twice-weekly reporting possible should this be necessary.

The monitoring stations report on a weekly basis regarding the number of patients who have consulted the practice with influenza-like illness. The baseline measurement used for the incidence of influenza-like illness is 5.1 per 10,000 people. There is evidence of 'increased influenza activity' when the incidence of influenza-like illness rises above the baseline measurement for a period of 2 consecutive weeks and when the influenza virus is found in the patient samples.

Since the influenza season of 1992/1993, all monitoring station doctors have also been requested to take nose-throat swabs in a random sample of patients with influenza-like illness. For this purpose, at least 2 samples per week should be sent for testing, including 1 from a child. Should there be no or insufficient patients with influenza-like illness in the week in question, then samples may be taken from patients with an acute or other type of respiratory infection. The nose-throat swabs are sent to the NIC at the RIVM for laboratory investigation. Using molecular methods, the samples are tested for the presence of respiratory viruses that include influenza viruses and respiratory synctyial virus as well as atypical bacteria. The number of pathogens sought out by laboratory analysis can vary from year to year. Isolated influenza viruses subsequently undergo antigenic and molecular characterization by the NIC-EMC.

On August 21, 2009, 20 general practitioners were added to the CMR's network of monitoring stations.

Non-sentinel data collection encompasses the virological results of patient samples that have been tested for the presence of influenza virus and/or RSV that do not fall under the category of sentinel – as given below.

The weekly virological bulletins
In the weekly virological bulletins, a number of virology laboratories – who collaborate in the Dutch Working Party for Clinical Virology – report on the numbers of samples that test positive for various pathogens including those for respiratory conditions. This diagnostic testing is carried out using a variety of laboratory techniques, such as cultures, molecular diagnostics, serology and rapid testing. All positive diagnostic tests from the laboratories are reported on a weekly basis in the weekly bulletin. The reports are thus made according to the date, given as the week number of the laboratory diagnostic test. The weekly bulletins are sent to the RIVM where the data is processed. During the 2009 H1N1 pandemic, all samples found positive for the influenza A H1N1 virus were subject to an extra questionnaire that was drawn up to determine the age distribution of the patients and the source of the samples.

Data from EMC
The number of influenza strains for each type and subtype that were received each week by the EMC were put into an Excel spreadsheet and e-mailed to the EPI. The EMC collated this information from influenza isolates and clinical samples that had been sent for antigenic characterization.

CMR monitoring stations data
The EPI received weekly updates of virology results for patients with other acute respiratory infections from the CMR monitoring station surveillance of the NIVEL. This data does not, however, fall under the regular sentinel network.

5.2 Diagnostics

5.2.1 International

On June 23, 2009, the ECDC situation report referred to the WHO guidelines relating to the 2009 H1N1 pandemic virus [B, June 23, 2009].

5.2.2 National

The case definitions were not revised by the CIb during the period from June 9 to June 23, 2009.

On June 10, 2009, a new improved form – which was easier to read – for requesting laboratory diagnostics was distributed through Inf@ct. The form was coloured light yellow, for easy recognition, and was included in the standard RIVM sample-taking

packages from that date. In addition, after consultation with the LIS and the LCI, the time for deploying diagnostic tests was brought forward. From June 10, 2009 onwards, any samples that were received by the RIVM before 8 a.m. were investigated the same day. This meant that the laboratory results were also available earlier than before which reduced the amount of work that had to be done in the late evening. Samples could still be delivered to the RIVM 24 hours a day [C, June 10, 2009]. However, it was reported in the response team meeting of June 10, 2009 that the workload at the LIS was heavy. In the same week, issues surrounding the scaling up operation of the laboratories were also discussed [E, June 10, 2009].

On June 11, 2009, following questions from professionals in daily practice, the LIS conveyed in an Inf@ct message that it was still necessary to disinfect any material used when taking samples – such as scissors and culture tube – in spite of the fact that the procedure for the required protective measures had been simplified. Furthermore, the LIS announced a new telephone number where the samples could be registered 24/7. The samples had to be registered by telephone, both in and out of office hours, so that they could be analyzed in the morning round without further delay [C, June 11, 2009].

On June 16, 2009, the GGDs were requested via Inf@ct not to take samples from all contacts of contacts of an index case without further indication to do so. At a few regional GGDs, for logistical reasons, it had become normal practice to take samples from the direct contacts (family members) of the contact at the same time as taking samples from the contact of the index case. The LIS and the LCI asked for this practice to be limited, considering that a relatively small number of the contacts were actually found to test positive for the virus. If samples were taken, however, then professionals were requested to only send these extra samples for diagnostic testing if the original contact was found to be positive. The reason for this was that it could otherwise lead to logistic and administrative problems at the LIS. The LIS made a further announcement that as from June 16, 2009 onwards, the GGDs did not need to register the samples with the LIS [C, June 16, 2009]. As far as epidemiology was concerned, it remained important to have some insight into transmission risks, and for this purpose a selection of contacts was followed and sampled. The regional GGDs were supported in this task. Later on, this was also included in the supporting study funded by the Netherlands Organization for Health Research and Development (ZonMw).

By mid June 2009, the number of samples that the LIS was receiving for diagnostic testing had greatly increased. The LCI and the LIS again repeated the rules for diagnostic testing in an Inf@ct message on June 19, 2009; this was done to help the logistic process to run smoothly. The rules repeated the message that the regional GGDs should consult with the LCI prior to considering diagnostic testing. If a decision was made to continue with diagnostic testing, then the LCI would register the data for the LIS. This meant that the GGD no longer needed to register samples separately with the LIS. In the same Inf@ct message, the GGDs were told that they did not need to take samples from contacts of asymptomatic close contacts of a confirmed index patient. The testing of the many contacts of asymptomatic close contacts was causing a backlog in the LIS and LCI systems. If an asymptomatic contact did turn out to be positive to infection with the virus, then the prophylactic dose of oseltamivir was transposed into a therapeutic dosage [C, June 19, 2009].

On June 17, 2009, the LIS distributed new protocols, PCR kits, positive control and quality control (EQA panel) to the outbreak assistance laboratories. In addition, the other microbiology laboratories were sent the same material after requesting it as a response to the Labinf@ct message sent on June 5, 2009.

On June 18, 2009, the LIS advised laboratories in the Netherlands via Labinf@act against ceasing diagnostic testing for influenza A during the summer months – which was the normal procedure. In addition, it was pointed out to the laboratories that the new protocols for specific detection and identification of the 2009 H1N1 pandemic flu virus would be available for downloading from the CIb website later in the same week [D, June 18, 2009].

On June 19, 2009, the laboratory form that regional GGDs used for requesting diagnostic tests was changed again and distributed by the LCI and the LIS (via Inf@ct). As well as some changes to the text itself, the Osiris number – which was relevant for clinical cases – was added and the question of whether the patient agreed to having personal details included in the record was removed. The new form could be recognized by its light green colour [C, June 19, 2009].

On June 19, 2009, in the meeting of the response team, the LIS announced that the re-sampling on day 5, within the framework of resistance monitoring, was not going according to plan [E, June 19, 2009]. In the response team meeting of June 22, 2009, the LIS said that very few diagnostic tests were being requested by microbiologists for flu cases whereby patients had pneumonia [E, June 22, 2009].

5.3 Control

5.3.1 International

On June 11, 2009, the DG of the WHO raised the level of the pandemic alert to phase 6. Furthermore, the DG of the WHO repeated its advice to countries that they should not close their borders and not to impose any restrictions on international trade and/or traffic, including the movement of persons. All over the world, countries were encouraged to assess their own country's situation and to prepare themselves for the changeover from the containment phase to the mitigation phase [A, June 11, 2009; C, June 11, 2009].

During the three previous pandemics, pregnancy had been seen as a risk factor. According to the ECDC, the limited data that was available on the 2009 H1N1 virus reflected a similar risk [B, June 18, 2009]. To this end, in the light of the pandemic, the EMEA published a report on the use of oseltamivir for women during pregnancy or when breastfeeding and for children under the age of 1 year. For these patient groups, based on the existing literature, the EMEA concluded that the therapeutic and prophylactic use of oseltamivir was permissible. The EMEA's recommendation relating to the treatment of infants (< 3 months) was to always treat them in a hospital setting. The EMEA was explicit in stating that this applied to the 2009 H1N1 pandemic situation at that particular time. The conclusion of the EMEA was based on clinical data from 232 pregnancies. In the case of a pandemic situation occurring, the advantages of administering oseltamivir outweighed its disadvantages [C, June 12, 2009]. On June 18, 2009, the ECDC referred to an article by Tanaka et al. which described the safety of using neuraminidase inhibitors and the absence of teratogenic effects (i.e. those giving rise to deformities) associated with these drugs [21]. This study confirmed the decision made by both the Food and Drug Administration (FDA) and the EMEA that allowed neuraminidase inhibitors to be used for/by pregnant women during the 2009 H1N1 pandemic [B, June 18, 2009].

From June 15, 2009 onwards, the CDC decided not to test everyone who showed influenza-like symptoms because the workload in the US laboratories was very high. This meant that there was an even greater risk that people with influenza-like symptoms were actually infected with the 2009 H1N1 virus [B, June 15, 2009].

On June 23, 2009, the ECDC published the CDC guidelines for reducing the risk of 2009 H1N1 flu transmission in health care institutions. What led to this were the first signs of the 2009 H1N1 virus occurring in health care workers. Some of these employees working in the health care sector had contracted the infection whilst they were at work. However, in the US and in Europe the authorities were often unable to achieve consensus as to whether or not the use of N95 masks or surgical masks was recommended or compulsory in certain high risk situations [B, June 23, 2009]. In an article by Phin et al., the wearing of masks by professionals while carrying out routine tasks in health care institutions was described as likely to be impractical [22].

Policy measures for outbreaks on cruise ships: The policy measures that need to be taken for an outbreak of pandemic influenza that occurs on board a ship during an international trip, are regulated by the 2005 International Health Regulations (IHR). A country's competent authority may refuse the departure or arrival of a ship on the grounds of national legislation or in accordance with the 2005 IHR [B, June 18, 2009].

5.3.2 National

On June 10, 2009, after consultation between the CIb and the Dutch Working Party on Infection Prevention (WIP) it was decided that the infection prevention policy for the 2009 H1N1 virus should be harmonized with that for the regular seasonal influenza. This was decided on the basis of advancing insights into the relatively mild disease symptoms caused by the H1N1 infection. Among other things, this meant that wearing gloves and an FFP1 mask – or equivalent – was sufficient when taking samples from patients. In addition, family contacts were no longer required to wear a mask when in direct contact with the patient but they were given prophylactic oseltamivir. Patients who did have symptoms had to remain at home in isolation for the duration of the antiviral treatment and while they were waiting for the results of the laboratory tests to come through. The justification for this change in policy was explained in a document that was sent as an attachment to an Inf@ct message on June 10, 2009. The most important reasons for the initial strict infection prevention policy related to the fact that little was known of the virus itself and all those involved with its control were keen to prevent it entering the Netherlands for as long as possible. The information for patients and contacts that was available on the CIb's flu website was changed to accommodate the new prevention policy [C, June 10, 2009].

On June 10, 2009, the LCI also announced the revised policy for asymptomatic persons who were confirmed cases of 2009 H1N1 infection. This was done because it was possible that samples taken from contacts who were asymptomatic could still test positive for the virus. In these cases, the policy was to change from a prophylactic oseltamivir dose – which the person was already taking due to his/her close contact with a confirmed patient – to an oseltamivir treatment regime. As long as the person concerned remained asymptomatic, he/she was allowed to move around freely; however, as soon as symptoms occurred, and irrespective of whether or not these met the criteria of the clinical case definition, this person had to remain at home. The CIb assumed that asymptomatic infected persons hardly contributed to the spread of the virus, certainly not when they were being treated with oseltamivir. For this reason, no further contact investigation was conducted in asymptomatic infected persons [C, June 10, 2009].

The WHO's decision to raise the level of pandemic alert – taken on June 11, 2009 – did not have any direct consequences for the policy in the Netherlands [C, June 11, 2009]. In fact, at this time, the CIb had already started preparations for changing over to the mitigation phase [C, June 8, 2009]. During the meetings of the response team, it was pointed out that the workload at the regional GGDs, the NVI and the

RIVM departments under the former control policy had been extremely high. The upscaling operation at the LCI was in full swing and there were three fulltime on-duty staff members concentrating on the 2009 H1N1 pandemic. For this reason, from June 10, 2009, the Regional Consultants Communicable Disease Control (RACers) were deployed to support the LCI with its tasks. Outside office hours, there were always two people on stand-by duty. The extra support from desk editors, communication and secretarial staff continued. At the EPI, there was also a re-prioritizing of people and activities to support the surveillance and epidemiology of the 2009 H1N1 pandemic and also to support the LCI and the LIS with the flu surveillance and the development and management of the database. The diagnostic work being conducted at the LIS was supported by researchers from various virological projects.

On June 11, 2009, the LCI announced through Inf@ct that patients in home isolation were no longer required to wear a mask. The guiding principle for this measure was that the patient's family contacts were protected against the virus through antiviral prophylaxis and the care professionals were protected by wearing a mask and gloves. On June 12, 2009, the LCI communicated that patients with positive results must stay in home isolation for a period of 10 days following the first day of illness. This home isolation could end only if the result of the sample taken on day 5 was found to be negative [C, June 12, 2009].

The guidelines for the dosages of oseltamivir for children were communicated by the LCI via Inf@ct on June 12, 2009. This followed the EMEA's approval of the prophylactic use of oseltamivir – therapeutic use of this drug had been approved earlier – for pregnant women, women who were breastfeeding and children under the age of 1 year. The prophylactic treatment of children under the age of 1 year consisted of 2 to 3 mg/kg body weight for a period of 10 days. The therapeutic treatment of children under the age of 1 year consisted of 2 to 3 mg/kg body weight twice daily for a period of 5 days. The decision to administer oseltamivir had to be taken by a doctor, in some cases after consultation with a paediatrician. The patient leaflet for Tamiflu® was placed on the CIb's flu website. The medication was still only available through the LCI, or outside office hours through the doctor on duty at the LCI. In these cases, the NVI delivered the oseltamivir to the relevant GGD or outpatient department [C, June 12, 2009].

On June 12, 2009, the Netherlands Ministry of Foreign Affairs lifted the restrictions applying to trips to and from Mexico that had been in place since April 29, 2009. Based on the epidemiological situation at the time, the advice to refrain from non-essential travel to Mexico was withdrawn [C, June 12, 2009].

A course of treatment with oseltamivir should preferably be started within 48 hours of the onset of symptoms. In day-to-day practice, however, this was often not possible as doctors had to wait until the result of the laboratory tests was known before starting treatment. Therefore, on June 15, 2009, the CIb decided that patients who met the clinical and epidemiological criteria of the case definition should be started on treatment with oseltamivir as soon as samples had been taken instead of waiting for laboratory confirmation. This did not apply to prophylactic treatment for close contacts; in these cases, treatment should only start after the diagnosis in the index case had been confirmed [C, June 15, 2009].

On June 16, 2009, the LCI announced via Inf@ct that regional GGDs that were distributing oseltamivir were no longer required to do this through the LCI; however, they were still required to register any drugs issued [C, June 16, 2009].

On June 17, 2009, the questionnaire in Osiris relating to underlying conditions and a follow-up on complications, pregnancy, antiviral treatment, hospital admission and death was revised by the CIb. For hospital admission cases, questions on ICU admission and mechanical ventilation were added. These changes to the Osiris questionnaire were made in order to improve the information included in international reports. In addition, the EPI and the LCI wanted to improve the monitoring of disease burden and complications in patients. To this end, the regional GGDs were asked (in an Inf@ct message of June 19, 2009) to monitor and register in Osiris the recovery and/or any complications affecting patients with 2009 H1N1 flu at 7 to 10 days after the onset of symptoms; this applied in particular to patients with more severe disease symptoms. With regard to this registration, it was important that the GGDs only finalized the registration in Osiris once the follow-up had been filled out. The GGDs were requested by e-mail to submit the follow-up data for those cases already registered in Osiris. In the same Inf@ct message, the GGDs were once more reminded to provide as much detail as possible in respect of the requested personal data of patients (date of birth, postal code and BSN number) on the laboratory request form and in Osiris. This was important for linking the laboratory information to the epidemiological data [C, June 19, 2009].

On June 18, 2009, the Pandora system (version 2.5) became operational.

Pandora The Pandora system dates back to 2003 and the outbreak of avian influenza in the Netherlands. Since that time, various parties have worked to develop this automized system further. The objective is to be able to access information quickly for outbreak and analytical investigation in the event of a future outbreak of avian or pandemic influenza. Pandora had hardly been used at all prior to the 2009 H1N1 influenza pandemic. During this outbreak, Pandora was initially not used because the system was not ready for immediate use. The EPI and EMI departments at the RIVM worked very hard to get the system up and running within a short space of time. Technical adjustments needed to be implemented by the EMI in order to respond well to the 2009 H1N1 pandemic situation. On June 18, 2009, the Pandora system (version 2.5) became operational. On June 29, 2009, epidemic or epi curves could be made in Pandora (version 2.6) and on July 14, 2009, the data from the outbreak assistance laboratories became available in version 2.7. Due to the changes made to the case definition on August 15, 2009, the option of making charts and maps with the Geographic Information System (GIS) was enhanced. At first, the GIS maps were made by the Centre for Public Health Forecasting (cVTV) of the RIVM where data was received from the EPI. As well as the epi curves for the number of hospital admissions, epi curves for the number of ICU admission and deaths were also needed. These options were added and from that point in time they were used for the CIb weekly reports that appeared on their theme website and were also distributed internally. After August 15, 2009, the options for making GIS maps were also enhanced. As soon as these GIS functions became operational in Pandora, the GIS maps were also actually produced in Pandora and no longer made by the Centre for Public Health Forecasting.

On June 19, 2009, the LCI announced via Inf@ct that the Royal Dutch Pharmaceutical Society (KNMP) had noted that the regional GGDs were not always being consistently careful with their issuing of oseltamivir – especially where children were concerned. The LCI advised the GGDs to act scrupulously where the issuing of this drug was concerned and to consult with the pharmacist in charge if there was any doubt involved. Further, the LCI reported that for practical reasons some regional GGDs were delivering the children's dosages of oseltamivir to pharmacies in the neighbourhood of the patient. The KNMP responded to this by saying that the delivery of antiviral agents on prescription fell under the regular pharmaceutical care of a pharmacy. This meant that as well as implementing the necessary supervision, i.e. the monitoring of drugs, instruction et cetera, the pharmacy could also charge

the patient the rates as set by the Dutch Healthcare Authority (NZa). As well as the costs for the packaging, the patient would also be charged the dispensing fee that was set at a maximum of 11 euros (excluding low-rate VAT) for drugs dispensed for the first time. In principle, the same rules applied if a GGD used oseltamivir from a pharmacy. Finally, the LCI reported that the ordering form for oseltamivir had been revised. The regional GGDs were requested to e-mail the LCI a weekly overview (on Fridays) of their issuing of oseltamivir in their region, but only if the drug had been issued in the week in question [C, June 19, 2009].

The third meeting of the OMT for the 2009 H1N1 pandemic was held on June 22, 2009. The EPI had written a memorandum – translated as: 'Use of oseltamivir during the 2009 new H1N1 influenza pandemic in the Netherlands'. During this third OMT meeting, various issues came to light [G, June 22, 2009]:

- The GP monitoring stations had not noticed any increase in influenza activity in the Netherlands.
- Influenza had not been confirmed in people admitted to hospital with pneumonia of unknown origin.
- No clusters of influenza had been reported in institutions such as nursing homes.

The OMT recommended continuing the current policy of tracing new cases of infection with the virus, but ceasing the active search for contacts of cases, including air passengers. Members of the same household as patients were no longer given prophylactic treatment but were warned about the virus. These household members were given therapeutic oseltamivir if they developed disease symptoms; however, no diagnostic tests were required to be carried out, i.e. samples were no longer taken from contacts. If a household member became ill, then this did have to be reported as a suspect case in Osiris. Moreover, the period of 10 days home isolation for patients was ended. Once a patient had recovered, he was free to leave his home. As far as the re-sampling on the fifth day of illness was concerned, the OMT said that this measure could be limited although it should still be carried out in patients who were not recovering well; this was for the purpose of resistance monitoring. The OMT also recommended easing up the advice for the protective measures needed for health care workers when taking samples from patients. This meant that only the wearing of protective gloves and masks was required [G, June 22, 2009]. The OMT advised the WIP to think about the protective measures needed when performing procedures with a high risk of transmission on patients admitted to hospital [C, June 24, 2009]. All of the OMT recommendations were accepted by the BAO [H, June 23, 2009].

During the third OMT meeting on June 22, 2009, the option of closing down schools so that the transmission of the 2009 H1N1 virus could be restricted as much as possible was discussed. The EPI was working on a memorandum which justified the reasons why school closures and other measures aimed at social distancing were likely to result in a reduction of disease incidence, especially the peak incidence. In the EPI memorandum of August 13, 2009 which translates as: 'School closure during an influenza pandemic', the implementation, expected effects, the costs and the incidence threshold for school closure were discussed. However, it was not clear whether or not this measure could be applied successfully at the level of an individual school under the circumstances prevailing at the time. The OMT concluded that there was no justification for school closures and that more evidence was needed relating to the advantages and disadvantages of closing schools and the effects that this would have. The OMT expected this discussion to come up again in the autumn of 2009 [G, June 22, 2009].

5.4 Government communications

5.4.1 International

After the WHO had raised the level of pandemic alert on June 11, 2009, all European countries were given information on the pandemic situation through an official document distributed by WHO Europe. The document gave a detailed explanation of the reasons for raising the level of pandemic alert. The LCI sent this document to all parties concerned as an attachment of Inf@ct of June 12, 2009 [C, June 12, 2009].

On June 12, 2009, the ECDC revised its risk assessment for pandemic flu.

From June 15, 2009 onwards, the CDC published a summary for professionals on their website every Friday with information on the pandemic flu (www.cdc.gov/h1n1flu). Moreover, a more complete weekly summary on the 2009 H1N1 pandemic situation in the US could be found in the FluView report. Material used during press conferences with the CDC was also uploaded to the CDC website every Friday [B, June 15, 2009].

Due to the increasing number of outbreaks of the 2009 H1N1 virus on cruise ships, on June 18, 2009, the ECDC referred to the guidelines of the SHIPSAN TRAINET association [B, June 18, 2009]. The aim of these guidelines was to prevent the spread of influenza infections on cruise ships and ferries [23].

On June 20, 2009, the ECDC published its advice regarding school closures.

5.4.2 National

On June 10, 2009, researchers at the EPI were given access to the epidemiological data held by the Health Protection Agency (HPA) in the UK. This enabled closer monitoring of the 2009 H1N1 pandemic situation in the UK by the EPI.

On June 12, 2009, the RIVM issued a press release on the WHO's decision to raise the level of pandemic alert to phase 6. In this announcement, the public was once more reminded that travellers from the US and Mexico, who developed symptoms of fever and flu, must contact their GP by telephone. Travellers from other countries who also had such symptoms were advised to contact their GP if they had been in contact with a confirmed case of 2009 H1N1 flu [C, June 11, 2009].

On June 16, 2009, it was conveyed through Inf@ct that announcements about local clusters occurring in schools or other institutions would be made by spokespeople from the regional GGDs and not from the RIVM. The LCI encouraged the GGDs to provide GPs in the area where a cluster had occurred with information on the current situation. This was because GPs were being inundated with questions from worried parents and had to be kept up-to-date on all the pandemic facts so that they could give appropriate advice to their patients. At this time, there was still no substantial evidence to justify school closures. If a case of 2009 H1N1 flu occurred in a school, the GGD would make a risk estimate and give prophylactic treatment to any children who had a risk of infection. After consultation with the school, the GGD could – based on other arguments, such as anxiety – consider the option of telling parents to keep their children at home. This also applied to other activities such as school trips and parties. Each situation was different and required careful judgment on the part of the GGD involved. In the same Inf@ct message of June 16, 2009, the LCI also advised against the liturgical practice of sharing a common cup in church services; this had already been mentioned in media messages. At the time, the RIVM had also been receiving queries about this. This kind of situation required a response from the relevant local GGD, not from the RIVM [C, June 2009].

On June 18, 2009, the EPI published its first weekly CIb summary on the CIb flu website, translated as: 'Overview of 2009 H1N1 pandemic influenza patients' which could be found under the 'information for professionals' tab. The weekly summaries were also distributed via the expert meetings for disease detection and the *Netherlands Journal of Medicine* (NTvG).

Weekly CIb summaries on the CIb flu website

In the period from June 18, 2009 to December 31, 2009, weekly summaries of the cases of 2009 H1N1 influenza in the Netherlands were made by the EPI. Initially they contained the following items:

- the number of laboratory-confirmed cases;
- the clinical status of laboratory-confirmed cases;
- the epi curve for the first day of illness and import status;
- the number of laboratory-confirmed cases by GGD region and import status;
- the number of laboratory-confirmed cases by age and import status.

During the outbreak of the 2009 H1N1 influenza pandemic, the following items were added to the weekly summary:

- July 2, 2009 – Probable patient to health care worker transmission;
- July 9, 2009 – data from the CMR monitoring surveillance stations (NIVEL);
- July 16, 2009 – number of reported cases of the 2009 H1N1 pandemic virus worldwide;
- July 23, 2009 – summary/conclusion; distribution of countries where contamination had occurred;
- August 7, 2009 – underlying conditions in hospital admissions; age distribution of patients admitted to hospital because of a laboratory-confirmed infection with the 2009 H1N1 pandemic virus; mortality data including all causes per week;
- August 13, s 2009 – surveillance of virology laboratories;
- August 27, 2009 – data from the surveillance network for infectious diseases in nursing homes (SNIV); number of admissions per GGD region; number of hospital admissions by admission day;
- September 3, 2009 – pregnancy as reported in underlying conditions for hospital admission; distribution of hospital admission per day; age distribution of patients admitted to hospital; admission to an ICU; underlying conditions/pregnancy for ICU admissions; resistance of 2009 H1N1 influenza viruses;
- September 10, 2009 – admissions to a paediatric ICU;
- September 24, 2009 – subtypes of influenza viruses received by the NIC;
- October 1, 2009 – age distribution of patients with an infection of 2009 H1N1 virus infection, data from virology laboratories;
- October 8, 2009 – gender distribution for patients admitted to hospital;
- October 16, 2009 – prescribed dosages of oseltamivir;
- October 30, 2009 – underlying conditions of deaths; data from the 'Big influenza survey' (Grote-Griep-meting).

On June 19, 2009, the LCI distributed (via Inf@ct) a PowerPoint presentation and a letter of information for schools that had a confirmed case of 2009 H1N1 influenza [C, June 19, 2009]. The PowerPoint presentation was compiled by the regional GGD for Midden-Nederland; the letter of information was compiled by the LCI [C, June 24, 2009].

Around June 22, 2009, the new posters and flyers with information on the revised policy for contact investigation were displayed at Schiphol airport. Travellers were alerted to the risks of infection with the 2009 H1N1 pandemic virus. Advice was also

given to travellers on how they should act if they developed symptoms [E, June 22, 2009].

5.5 Meetings

5.5.1 International

On June 11, 2009, the fourth meeting of the WHO Emergency Committee was held. Following this meeting, the DG of the WHO raised the level of pandemic alert from phase 5 to phase 6.

5.5.2 National

On June 22, 2009, the third meeting of the OMT for the 2009 H1N1 pandemic was held [G, June 22, 2009]. All the recommendations from the third OMT meeting were adopted in the third meeting of the BAO that took place on June 23, 2009 [H, June 23, 2009].

5.6 Vaccination policy for the 2009 H1N1 virus

5.6.1 International

On June 9, 2009, the European Commission issued a press release calling for solidarity in the distribution of vaccines on the part of those countries that had already ordered vaccines [F, June 10, 2009].

On June 11, 2009, the WHO announced through its website that they were in close contact with the vaccine manufacturers. According to the WHO, the production of vaccines for seasonal influenza was nearly complete. 'The full production capacity will be available shortly to ensure the largest possible supply of pandemic vaccine in the months to come', WHO statement [A, June 11, 2009].

5.6.2 National

On June 18, 2009, in a letter to the House of Representatives, the Ministry of VWS announced that Minister Klink had ordered 34 million vaccines for the 2009 H1N1 pandemic virus from the vaccine manufacturers Novartis and Glaxo Smith Kline. This number had been ordered so that the entire population of the Netherlands and the Dutch Antilles could be given two vaccinations if this was found to be necessary [F, June 19, 2009].

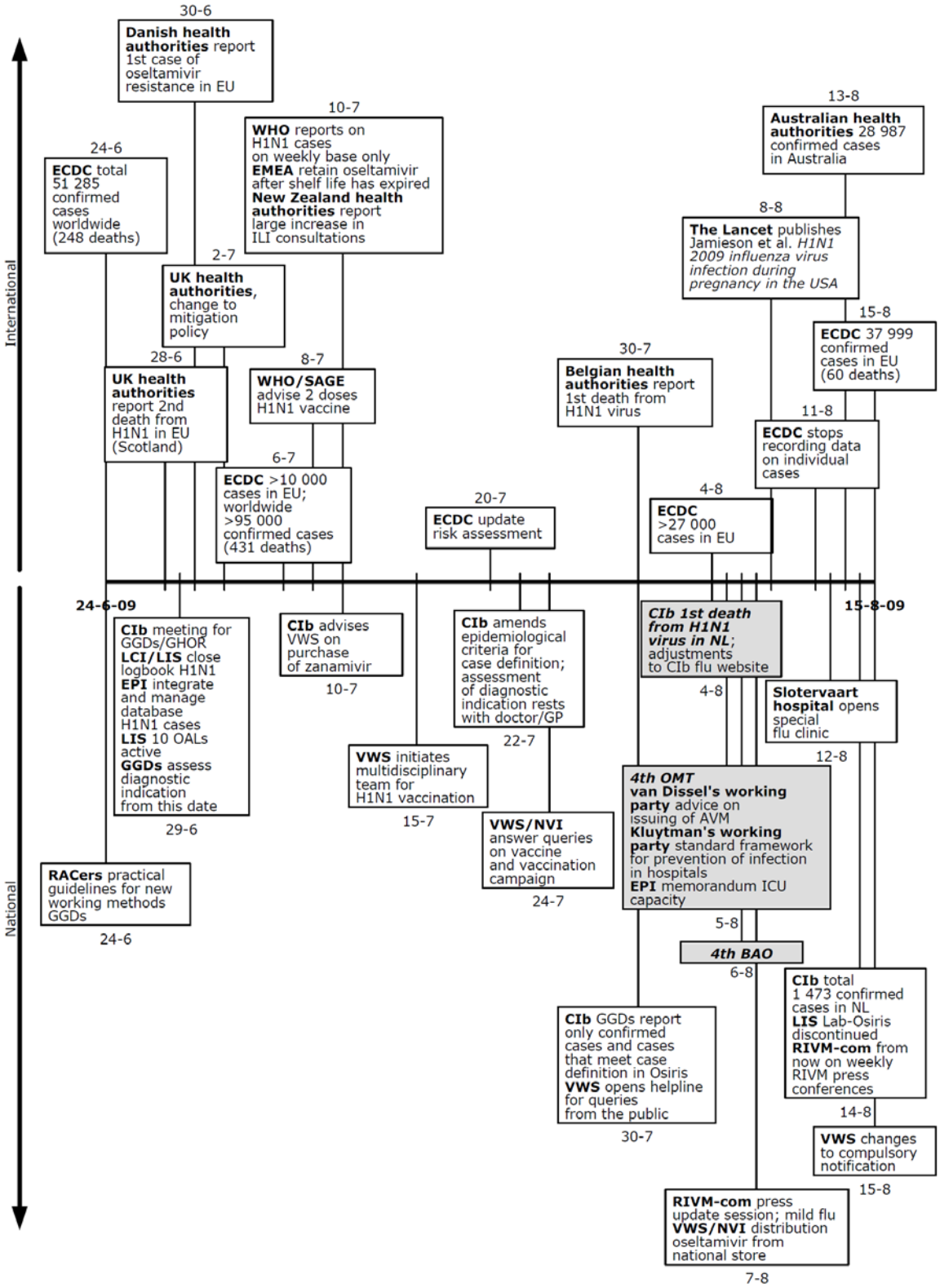

Figure 5 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period June 24, 2009 to August 15, 2009.

6 Period 4: from June 24, 2009 to August 15, 2009

Transition to mitigation policy in the Netherlands
In the Netherlands, the fourth period of the influenza pandemic was characterized by a change in control policy. Preventing the spread of the pandemic influenza virus was no longer considered an objective, and the policy was changed to one of containing the spread through mitigation measures. August 4, 2009, saw the first death of an H1N1 influenza patient in the Netherlands; this patient also had extremely severe underlying conditions. In most cases, however, the illness was mild and comparable to seasonal influenza. Towards the end of period 4, the compulsory notification for 2009 H1N1 pandemic influenza was changed: after August 15, 2009, only cases of laboratory-confirmed infection with influenza A or the new 2009 H1N1 pandemic virus in patients admitted to hospital and/or those who had died were subject to compulsory notification.

6.1 Situation

6.1.1 International

On June 24, 2009, a worldwide total of 51,285 cases (including 248 deaths) of 2009 H1N1 pandemic flu had been reported to the ECDC. At that time, there were 4844 reported cases in Europe, including 1 reported death in the United Kingdom [B, June 24, 2009]. On June 26, 2009, the WHO described the flu as 'a mild pandemic' as it had also announced on June 11, 2009 in the WHO statement explaining the pandemic alert phase 6. According to the WHO, a mild pandemic was characterized by the following [B, June 26, 2009]:

- most people would recover from the infection without needing to receive medical care or be admitted to hospital;
- in general, at national level, the number of people with severe 2009 H1N1 flu illness was comparable to the number of people affected by seasonal influenza – although the number of people affected was very high in some areas and in some institutions;
- the hospitals and health care institutions in the affected countries could, in general, cope with the care demand – in spite of the fact that some areas and institutions had heavy workloads.

In the weekly report from the European Influenza Surveillance Network (EISN), for week 25 published on June 26, 2009, low influenza activity was reported in all European countries. According to the ECDC, this reflected a low circulation of the 2009 H1N1 pandemic virus and other influenza viruses in the population. However, there was an increase in the number of cases of influenza-like illness seen in some of the sentinel networks which compared with the previous week [B, June 26, 2009].

On June 28, 2009, the second death in Europe resulting from infection with the 2009 H1N1 pandemic virus was reported to the ECDC. This was the death of a 73-year-old man from Scotland who had severe underlying conditions and who died 15 days after admission to the ICU [B, June 28, 2009]. On June 30, 2009, the third death in Europe resulting from infection with the 2009 H1N1 pandemic virus was reported to the ECDC from Spain
[B, June 30, 2009].

On July 1, 2009, the ECDC reported 601 new cases of 2009 H1N1 pandemic flu in the UK that had occurred in the previous 24 hours. At the time, there were a total of

8890 cases in Europe, which included 4 deaths; the total number of deaths worldwide up to that point was 332 [B, July 1, 2009].

On June 6, 2009, the WHO reported that worldwide there had been 95,824 cases of 2009 H1N1 flu confirmed which included 431 deaths [B, July 6, 2009].
In New Zealand there was a sharp increase in the number of consultations for influenza-like symptoms (measured through the national sentinel surveillance systems) around July 10, 2009. These figures (184 in 100,000) were much higher than those for the 2 previous years and were still increasing. The predominating strain that was being identified in the samples from the sentinel population and the laboratories' surveillance was that of the 2009 H1N1 pandemic virus, although there was sustained transmission of seasonal influenza at the same time [B, July 10, 2009].

In early July 2009, influenza A H1N1 virus strains that were resistant to oseltamivir were found in Denmark (reported on June 30, 2009), Japan and Hong Kong [C, July 10, 2009]. The case in Denmark was a patient who had been treated because he had been in contact with a number of people who had flu that was caused by the new 2009 H1N1 virus [B, June 29, 2009]. The patient was tested for the virus because, in spite of having had treatment for 5 days, he still developed flu symptoms. This patient did, however, make a full recovery and no new contacts became infected with the resistant virus. The LIS reported in an Inf@ct message that the development of resistance to oseltamivir in influenza viruses had been described before, so that what had happened here was not really unexpected. According to the LIS, the influenza viruses that had mutated and become resistant to antiviral drugs in the past had been characterized as being less well transmitted from human to human. However, in recent years, drug-resistant influenza viruses subtyped as H1N1 were circulating in the population and could spread just as easily as the non-resistant virus from which it had mutated. With this in mind, the importance of diagnostic testing of patients who had not responded sufficiently to treatment after taking oseltamivir for 5 days became clear [C, July 10, 2009].

Around July 14, 2009, three deaths (including one of a GP) caused by infection with the 2009 H1N1 pandemic virus were discussed in the British and international press. None of these three people had been suffering from an underlying condition. According to the ECDC, during an influenza pandemic or outbreak of seasonal influenza, it was not unusual for some people who had previously been healthy to become seriously ill and/or die as a result of infection. The message conveyed by the ECDC was that health care workers are always at risk of contracting an infection for as long as the pandemic continues. For this reason, health care workers were also requested to take the appropriate protective measures when they had contact with patients who might be infected with the virus [B, July 14, 2009].

On July 17, 2009, in its weekly pandemic flu update, the HPA in the UK reported that the number of GP consultations for an influenza-like illness were higher than those usually seen for seasonal influenza. In fact, the figures were higher than those for the peak influenza activity for the winter of 2008-2009. The HPA also announced that children and adolescents were particularly affected by the 2009 H1N1 pandemic virus [B, July 17, 2009]. One week later, the HPA reported an unusually high incidence of influenza-like illness in all regions of the UK, adding and that the age group of 0-14 years was the worst affected. The disease itself remained mild in character [B, July 23, 2009].

On July 24, 2009, the ECDC weekly report with the title 'Pandemic (H1N1) 2009: Analysis of individual case reports in EU and EEA countries' stated that the

percentage of hospital admissions directly resulting from the 2009 H1N1 pandemic virus in EU and EFTA countries had increased since June 15, 2009. In general, hospital admission due to an infection with the 2009 H1N1 virus was seen most in people in the age category of 20-29 years. This was concluded from individual data taken from 8936 confirmed cases of 2009 H1N1 flu which had been reported by 28 EU and EFTA countries; of all these cases, 67% were reported in the UK. In the CDC's MMWR for that week, an article was published on the clinical findings in 4 children who had sustained neurological complications following infection with the 2009 H1N1 virus [B, July 24, 2009].

On July 30, 2009, Belgium reported the first death resulting from the 2009 H1N1 pandemic virus.

On August 4, 2009, the ECDC reported that in Europe there were a total of more than 27,000 patients with the 2009 H1N1 pandemic virus as confirmed by laboratory tests.

On August 7, 2009, the EISN reported in its weekly bulletin that all of the 84 subtyped influenza viruses that had been detected in the sentinel networks in week 31 of 2009, were those of the 2009 H1N1 pandemic virus. At this time, the UK reported moderate influenza activity – as opposed to the high activity of previous weeks – for the first time [B, August 7, 2009].

On August 8, 2009, an article by Jamieson et al. on the complications of the 2009 H1N1 pandemic virus in pregnant women was published in *The Lancet* [24]. This study, based on the first 34 hospital admissions of pregnant women who were infected with the 2009 H1N1 virus, found that they had an increased risk of hospital admission compared to other women of the same age and women in the general population [B, July 29, 2009].

On August 13, 2009, there were 28,987 cases of the 2009 H1N1 pandemic flu in Australia; this total included 102 deaths. The number of deaths resulting from the new virus continued to increase. Worldwide, 1906 people had died (including 55 in Europe) as a result of an infection with the new virus [B, August 13, 2009].

On August 15, 2009, there were 37,999 cases confirmed in Europe, which included 60 deaths. Outside Europe, at that time, the ECDC had reported a total of 2013 deaths as a result of the 2009 H1N1 pandemic virus [B, August 15, 2009].

6.1.2 National

On June 26, 2009, a total of 118 cases of H1N1 pandemic flu had been confirmed in the Netherlands [E, June 26, 2009].

On July 10, 2009, there were 152 laboratory-confirmed cases of 2009 H1N1 pandemic flu in the Netherlands, 58 of which had become infected in the Netherlands. Due to the changed policy of contacts no longer being tested as a matter of course, fewer cases of infection with the virus were being identified [C, July 10, 2009].

On July 17, 2009, the regional GGDs in the Netherlands were brought up to date on a cluster that had been found in Groningen, a province in the north of the Netherlands. From a group of 25 students at the University of Groningen, 4 had been diagnosed with the 2009 H1N1 pandemic virus following a study trip to Argentina. By July 17,

2009, 5 regional GGDs were involved in the response to this cluster: Drenthe, Twente, Nijmegen, Friesland and Groningen [C, July 17, 2009].

On July 24, 2009, via an Inf@ct message, the GG&GD (equivalent to the GGD in other regions) of Utrecht conveyed information relating to 2 clusters of 2009 H1N1 pandemic flu in the city. One of these clusters was related to Europe Cantat – a singing event involving 3000 people from all over the world, but especially Europe. The second cluster had occurred in a student association in Utrecht. This association had organized a whole range of festivities lasting 10 days in which approximately 2000 people had participated. It was this second cluster of infections in particular that led to many questions among the participants. GPs were overrun with questions and the after-hours medical posts in the province of Utrecht were consulted very frequently. Many GPs subsequently sought contact with the GG&GD. The members of the student association were informed via e-mail. The GPs in the region of Utrecht were brought up-to-date on the situation through the GG&GD Utrecht and the GGD of Midden-Nederland. The most important activities of the GG&GD consisted of informing and reassuring everyone involved in the pandemic [C, July 24, 2009].
By mid July, 2009, the number of people reported as being infected with the 2009 H1N1 pandemic virus increased sharply. On July 24, 2009, there were 273 confirmed cases in the Netherlands and in the space of just one week, 76 new laboratory-confirmed cases had been registered in Osiris. Cases of illness that were related to large public events, such as that in Utrecht and the long distance walking event in Nijmegen, generated the greatest unrest in the general public (partly because they attracted a lot of media attention) and thus required a great deal of support from the GGDs involved [C, July 24, 2009]. The number of hospital admissions for people infected with the 2009 H1N1 flu virus remained very low [E, July 18, 2009]. On July 28, 2009, there had been 5 hospital admissions and 8 cases of pneumonia resulting from the H1N1 flu virus were reported [E, July 28, 2009]. On July 31, 2009, there were 517 possible cases of pandemic flu reported in the Netherlands [E, July 31, 2009].

On August 4, 2009, the first death of a patient with 2009 H1N1 pandemic flu occurred in the Netherlands, this patient did have severe underlying conditions.

On August 4, 2009, there were 663 confirmed cases in the Netherlands of which 9 were admitted to hospital [E, August 4, 2009]. On August 11, 2009, the number of confirmed cases had risen to 1012 and 219 of these people had acquired the infection in the Netherlands [E, August 11, 2009]. On August 4, 2009, the CIb reported that in most cases the disease was mild and could be compared with that of seasonal influenza: they said ‘Someone who contracts the 2009 H1N1 flu virus is ill, on average, for about a week. Even without taking any drugs, people who have this illness will recover quickly. Nonetheless, for some groups of people, the flu could be more serious’ said the CIb.

On August 5, 2009, through Inf@ct, the GGD IJsselland reported a new cluster of cases that had occurred during a children’s camp in Overijssel. At this camp for 96 children from all over the Netherlands, the spread of the H1N1 pandemic virus was observed in both supervisors and children. This cluster had probably been caused by one of the supervisors who was also a member of the student association in Utrecht where a previous cluster had broken out. The camp was brought to an end prematurely on August 4, 2009 and all participants were requested to contact their GP from home within 7 days if they showed any signs of flu symptoms developing [C, August 5, 2009].

On August 14, 2009, there were 1473 confirmed cases of 2009 H1N1 pandemic flu in the Netherlands and 289 of these had contracted the infection in the Netherlands. The patients in the Netherlands had mainly contracted the infection during trips to Spain or Greece. However, the percentage of 2009 H1N1 flu-positive samples from the CMR monitoring stations at that time was only about 13%. It was not clear what percentage of people with influenza-like illness were consulting their GPs at this time [E, August 14, 2009]. In comparison, for the whole respiratory season of 2008/2009, an influenza virus had been found in 21.8% of people with influenza-like illness, and at the peak of this period the percentage was 47.2%.

Percentage of positive influenza virus cultures for the season 2008/2009
Over the whole respiratory season 2008/2009 an influenza virus was found to be present in 21.8% of patients with an influenza-like illness. In the weeks in which the number of consultations for influenza-like illness was above the baseline (week 47 of 2008 up until week 8 of 2009) an influenza virus was detected in 37.4% of the patients with influenza-like illness and at the peak (week 3 of 2009) in 47.2% of patients with influenza-like illness. As well as the influenza virus, the rhinovirus was the most commonly occurring pathogen [25].

Percentage of positive influenza virus cultures for the season 2009/2010
In the season 2009/2010, the H1N1 pandemic influenza virus was found to be present in 37.7% of patients with an influenza-like illness. In the weeks in which the number of consultations for influenza-like illness was above the baseline (week 42 up until week 50, 2009) the 2009 H1N1 pandemic influenza virus was detected in 42.7% of the patients with influenza-like illness and at the peak (week 46 of 2009) in 53.4% of the patients with influenza-like illness. As well as the 2009 H1N1 pandemic influenza virus, the rhinovirus was the most commonly occurring (16.4%) pathogen [25].

6.2 Diagnostics

6.2.1 International

On July 1, 2009, the ECDC published a threat assessment entitled 'First isolation of a secondary oseltamivir-resistant A(H1N1)v strain in Denmark'.

6.2.2 National

On June 24, 2009, the LCI and the LIS announced through Inf@ct that the logistic and administration procedures for virus notification and testing of new patients was being simplified. By creating a link between the various reporting systems, a single notification to the GGD's Osiris system should suffice for the regional GGDs [C, June 24, 2009].

The upscaling operation for diagnostic testing started on Monday June 29, 2009. From this date, the nine previously selected laboratories would also be carrying out tests for the 2009 H1N1 influenza virus. The GGDs could therefore now send samples to the outbreak assistance laboratory (OAL) in their own region. The LCI no longer needed to be consulted for an indication for diagnostic testing. The results of the 2009 H1N1 flu diagnostic tests were communicated by each laboratory directly to the person who had requested them. This was now possible because of the new system, Lab-Osiris that had also been activated on June 29, 2009. Therefore, the LCI no longer played a role in laboratory diagnostics. The regional GGDs were advised by the LCI to contact the OAL in their region in order to make arrangements about the communication of results – this was particularly relevant for evenings and weekends [C, June 25, 2009].

Lab-Osiris
During the preparations for the diagnostic upscaling operation, work was also continued on developing a temporary national database – Lab-Osiris. This database would enable the nine outbreak assistance laboratories to register the diagnostic data relating to positive samples. From May 1, 2009, the EPI provided support to the LIS regarding the design of Lab-Osiris. Lab-Osiris was put into use by the LIS and EMC to communicate laboratory results on June 17, 2009. The Lab-Osiris database was available to the outbreak assistance laboratories on June 29, 2009; this was the date when the OALs became activated. From that date, the results of the 2009 H1N1 influenza diagnostic tests were communicated by each laboratory directly to the person who had requested them. The demographic characteristics of patients were also entered in Lab-Osiris. The database was closed down on August 14, 2009.

As well as reporting the results directly to the person who had requested them, the OALs also used the Lab-Osiris surveillance system to report results to the RIVM. The national case register was based on data from sources that included both the GGD-Osiris and Lab-Osiris systems. The collective LIS/LCI logbook in which cases had been recorded up to that time, was closed down on June 29, 2009. There were a total of 925 cases registered in the collective LIS/LCI logbook. The logbook was integrated into the central databases that had been set up and maintained by the EPI [E, June 29, 2009].

The supporting study on the 2009 H1N1 pandemic virus was started on June 29, 2009.

Start of supporting study on the 2009 H1N1 pandemic virus
On June 29, 2009, the study entitled 'Supporting study on the 2009 H1N1 pandemic virus' was started. Many preparations were necessary prior to the start of this study. For example, the following documents were drawn up and revised: information on the participants, consent forms, basic information questionnaires, patient contact questionnaires, clinical diaries and patient contact diaries; in addition, the research sets were put together for the home visits. For this study, laboratory-confirmed patients were selected by the LIS from LIMS (the laboratory information management system of the LIS) and from Lab-Osiris. Subsequently, the CIb's research team (EPI, LIS, LCI) sought contact with the GGDs relevant to these selected patients. The GGD then approached the patient regarding the supporting study and informed the CIb's research team as to whether or not the patient, and where relevant close and/or household contacts, were prepared to participate in the study. An external diagnostic centre would then contact the patient to make an appointment for a home visit; this was based on a study schedule. During the home visit, the participants would be given information and instructions on the study and questionnaires were filled out and samples taken. The CIb prepared envelopes with all research material needed for a home visit.

On July 15, 2009, a request was made to the Medical Ethics Committee (METC) for an extension of the supporting study to include the academic medical centres in Utrecht, Rotterdam, Amsterdam, Leiden, Groningen, and Maastricht. On July 23, 2009, each centre was asked to send a statement to the METC relating to local feasibility. This meant that the Medical Ethics Committees at local level had to assess the study and this effectively delayed the start of the study. On September 21, 2009, the first local approval was received relating to the additional local feasibility study at the University Medical Centre Utrecht. On January 11, 2010, the final local approval for the local feasibility study of the 2009 H1N1 pandemic influenza supporting study was received from the Maastricht University Medical Centre.

Due to the changes in the compulsory notification for influenza, effective from August 15, 2009, it was no longer possible to include patients in the study through collaboration with the GGD. For this reason, it was decided to ask doctors from the NIVEL's CMR monitoring stations by

asking if they would extend their regular surveillance tasks by taking part in the supporting study on the 2009 H1N1 pandemic virus. On August 27, 2009, all doctors from the CMR monitoring stations were given written information on the aim and design of the study. In the week that followed, these doctors were contacted by the CIb's research team (by telephone) and asked whether they would take part in the supporting study – which would entail extra work on their behalf. The LIS selected patients from LIMS and if they met the inclusion criteria, the patient's GP was approached by the CIb's team. The external diagnostic centre then contacted the patient to arrange a home visit. Considering that the first sample from the patient was no longer obtained through the process of patient diagnostics but through the regular surveillance service, the study schedule had to be revised accordingly. This also meant that the research sets had to be adapted by the CIb research team.

The supporting study for 2009 H1N1 pandemic influenza was concluded at the end of March 2010.

At the end of June 2009, more samples from cases from the Dutch Antilles were investigated at the LIS and the EMC [E, June 29, 2009]. The number of samples sent from the Dutch Antilles at this time was in fact still increasing [E, July 28, 2009].

On June 30, 2009, through Inf@ct, the LCI circulated instructions for diagnostic testing for GPs. These instructions could be used by the regional GGDs if they were asked for further details by GPs [C, June 30, 2009]. Because many queries were still being received from GPs, an algorithm was also sent through Inf@ct as a complement to the instructions; this was sent by the LCI and the NHG to GPs in the Netherlands. The regional GGDs were advised to bring this algorithm into focus and adapt it to the local situation wherever necessary. Regarding questions about the methods used for the diagnostic tests themselves – for example, what type of cotton swab should be used? And how should the sample be sent? – the LIS had compiled a FAQ especially for GPs. All these products were placed on the websites of the CIb and the NHG [C, July 22, 2009].

On July 22, 2009, the LIS reported through Labinf@ct that, up to that point in time, drug resistance monitoring had been carried out for all new patients by sequencing patient material at the LIS. It was also reported that the EMC was developing a protocol for using PCR for the detection of resistance markers. Based on the preliminary data, a guideline was developed for the selection of patients for whom drug resistance measurement was indicated; standard protocols were also validated. The LIS and EMC were working on a proposal for standardized resistance and virulence monitoring in collaboration with the virology laboratories. Whilst waiting for this to be completed, laboratories could contact the LIS if they had any urgent questions regarding drug resistance measurement [D, July 22, 2009].

On July 22, 2009, through Inf@ct, the LCI conveyed the message that there were significant regional differences in the implementation of diagnostic testing. These differences were seen in the following areas: the person who took the samples (GP or GGD), where the sampling kits had been obtained, and the type of sample materials recommended by the laboratory. Some laboratories delivered sampling kits to all general practices, while others sent them by post as required. The LCI did not see this as a problem as long as all parties were aware of the agreed procedures which included the compulsory notification of confirmed cases. It was however, considered important for the relevant GGDs and laboratories to make agreements at local level with the GPs' representatives; in those cases where this had not already taken place, the GPs and after-hours medical posts had to be informed accordingly [C, July 22, 2009].

On July 22, 2009, the case definition for the indication for diagnostic testing was changed by the CIb. Clinical symptoms that met the flu criteria in people who had recently been to Mexico or the US were no longer an indication for diagnostic testing. This change was made because the number of countries reporting cases of 2009 H1N1 flu was rising sharply, and many cases in the Netherlands had been imported from countries other than Mexico and the US. The epidemiological part of the case definition was changed to 'a trip to an area in which sustained transmission of the 2009 H1N1 pandemic virus from human to human has been documented'. Subsequently, a reference was made to the CIb website which contained a map of the world (produced by the EPI) which showed the countries where more than 1000 patients had been diagnosed – this figure was seen as a rough estimate for sustained transmission. By dropping the artificial differentiation, the assessment of the necessity and the sampling for diagnostic tests fell under the responsibility of the treating physician, including the GPs in the regular health care circuit. This did not actually change the way people were treated. The GGD did continue to play a role in the diagnostics for clusters of the virus that occurred in institutions or child care facilities [C, July 22, 2009].

On July 24, 2009, the LCI made it clear via an Inf@ct message that as from July 22, 2009, any costs relating to diagnostics for individual patients had to be covered by the patient's own health care insurance. This also applied to the diagnostic testing carried out by the OALs. The costs associated with reference diagnostics at the CIb, which included the transport costs of the samples, were covered by the CIb. The costs of diagnostic tests requested by the GGDs for people in clusters, were paid for the patients [C, July 24, 2009].

On July 28, 2009, samples from five patients from Afghanistan were tested. The rapid tests for these five soldiers had been positive although the LIS only confirmed one of the samples as positive. According to the LIS, it was possible that the lengthy transport time had contributed to the negative results [E, July 28, 2009].

In the response team meeting of August 4, 2009, the LIS announced that the OALs were under pressure because of the large number of samples being sent in from the region. This extra heavy workload resulted in only a very limited number of samples being sent to the LIS for confirmation [E, August 4, 2009]. From August 7, 2009, the Lab-Osiris database became redundant and it was closed down on August 14, 2009. From that point onwards, the virological weekly bulletins provided information on the number of confirmed cases in the laboratories connected to the system [E, August 14, 2009]. For this purpose, after consultation with the CIb, the reporting system was temporarily enhanced, which meant that information was also available on a patient's age and the severity of the infection.

6.3 Control

6.3.1 International

In late June 2009, various regional GGDs reported to the LCI that holidaymakers on their way to Turkey were being stopped at the Bulgarian border and harassed with the following demands:

- a fine if they did not carry proof of vaccination against the 2009 H1N1 flu virus;
- a fine if they could not prove that they were not infected with the 2009 H1N1 flu virus;
- no border crossing if they had no proof;
- compulsory vaccination – otherwise no border crossing.

All of the above could be obtained at a price or bought off for a large sum. Through the Netherlands Ministry of Foreign Affairs, VWS contacted the Bulgarian embassy requesting them to revoke the border policy. It took a few days for this to happen. In the meantime, although it was not compatible with Dutch policy, individual regional GGDs were authorized to act at their own discretion to honour urgent requests for help from travellers [C, June 30, 2009].

From July 2, 2009, the control strategy of containment of the H1N1 flu virus in the UK changed because it was no longer considered realistic. Asymptomatic close contacts of infected people were no longer given prophylactic oseltamivir and were not always tested for the virus. This measure was intended to relieve the strain placed on the health care sector. Patients with uncomplicated symptoms were asked to stay at home [B, July 2, 2009]. On July 6, 2009, the health authorities in Denmark also announced that they were going to change their control strategy to one of mitigation [B, July 6, 2009].

On July 10, 2009, the EMEA indicated that it was not advisable to throw away any oseltamivir in view of the fact that this might lead to a shortage of the drug should a flu pandemic occur. This also applied to oseltamivir that had exceeded its 7 year shelf life (ref. EMEA/CHMP/27883P/2009). This meant that the NVI could still deliver Tamiflu® with an expiry date of July 2009 to the regional GGDs. The NVI asked the regional GGDs to use these packets of oseltamivir first, even if the date of July 31, 2009 had passed [C, July 10, 2009]. On July 30, 2009, the LCI advised the regional GGDs to change the expiry date on the packaging to December 31, 2009 on delivery. The NVI bore responsibility for the quality of the delivered batches [C, July 30, 2009].

On July 11, 2009, in their situation report, the ECDC referred to the PHAC's clinical guidelines relating to the treatment of pregnant women and women who were breastfeeding who had an influenza-like illness [B, July 11, 2009].

During the meeting of the response team held on July 18, 2009, it became clear that countries such as Ireland, Greece, and Belgium had already changed their policy to one of mitigation [E, July, 2009].

On August 13, 2009, the ECDC distributed three documents on vaccination, school closure and sick travellers.

6.3.2 National

The recommendations made by the third meeting of the OMT on June 22, 2009 were adopted by the third meeting of the BAO on June 23, 2009. This meant that the regional GGDs had to amend their work procedures once again. To accommodate the changes, the practical guidelines – which had been compiled by the RACers – for dealing with a possible case of flu, were amended and sent to the regional GGDs via an Inf@ct message on June 24, 2009 [C, June 24, 2009; C, June 25, 2009]. The third OMT meeting recommended discontinuing the active tracing of contacts; the policy for tracing new cases should, however, be continued [C, June 24, 2009]. The aim of this policy was to try to obtain information on the degree to which the virus was being introduced from abroad; this applied to the few areas that had sustained transmission but which had the highest incidence worldwide. The aim of this policy was to attempt to reduce virus transmission to the contacts who were at greatest risk, i.e. household members [C, June 25, 2009]. The OMT expressed its appreciation of the work being done by the regional GGDs and said that it was aware that many GGDs were being pushed to their limits. The OMT said that it would meet again to

revise the control policy as soon as there were indications of sustained transmission [C, June 24, 2009].

In late June 2009, the health authorities of Aruba discontinued their policy of entry screening. This led to the ending of the quarantine for the cruise ship Ocean Dream which was then in the Dutch Antilles [E, June 29, 2009].

From June 29, 2009 onwards, the LCI patient data form was taken out of use and the regional GGDs only needed to register cases in Osiris, because in the meantime there was one central database in which all data was collated and integrated. Moreover, the GGD-Osiris system was simplified. Questions relating both to exposure to contagious animal populations and to detailed sample information were dropped. The LCI advised the regional GGDs to add follow-up information to the notifications and make any necessary corrections. To this end, the regional GGDs were asked to contact the LCI straight away if a possible, probable or confirmed case of pandemic flu died and for any case involving 'patient to health care worker' virus transmission. The LCI also had to be informed of any clusters that occurred in the GGD region [C, June 25, 2009].

On July 10, 2009, the response team advised the Ministry of VWS to order zanamivir because it was possible that resistance to oseltamivir would develop. There was, in fact, the possibility of a supply of 400,000 doses of zanamivir becoming available in December 2009 [E, July 10, 2009]. But the Ministry of VWS delayed the purchase because it was expected that by December 2009 many people would already have been vaccinated. In addition, at the time, the Netherlands already had 500,000 doses of zanamivir in stock for use in an emergency which helped to sway the negative decision.

On July 10, 2009, the LCI shared the standard recommendations for dealing with large public events with the regional GGDs through an Inf@ct message. The regional GGDs could make use of this advice in their support for event organizers when they were making preparations for large events. When licenses for an event were granted, there was usually a stipulation that the organizer had to fulfil certain hygiene criteria. The principle underlying the standard recommendations was that large events could still be held at that time. However, any transmission that did occur had to be tackled as far as possible through effective hygiene measures and people with symptoms that fitted the pattern of an infection with the 2009 H1N1 virus had to be placed in isolation. The organizers had to consider any additional facilities or necessary measures together with the relevant GGD [C, July 10, 2009].

On July 15, 2009, the policy for dealing with the 2009 H1N1 virus during the long distance walking event in Nijmegen was compiled by the regional GGD of Nijmegen together with the RIVM, the GHOR and the organizers of the event; this information was then shared through Inf@ct with the other regional GGDs. Based on the LCI's standard recommendations for dealing with the new influenza virus during large public events, GGD Nijmegen had taken a number of measures to prevent the spread of the 2009 H1N1 virus. The emphasis lay on hygiene measures such as frequent hand washing and the use of paper tissues. During the event itself, a different case definition was applied – this was partly based on the situation and information from the home countries of the participants. In the event of walkers developing flu-like symptoms during the walk, they should report to a first-aid post along the route where a doctor would then decide whether the criteria of the case definition had been met. If the criteria of the case definition were met, then GGD Nijmegen would apply diagnostic testing and if necessary start treatment with oseltamivir. The patient was then sent home by private means of transport – i.e. not by public transport. If this

was not possible, for people who did not live in the Netherlands, for example, then the patient would be placed in isolation in a specially designed unit. For Dutch patients, GGD Nijmegen would subsequently pass on the results of the diagnostic tests to the patient and also inform the GGD in the patient's home town [C, July 15, 2009]. The preparations made for the Nijmegen walking event of 2009 were published in the *Infectieziekten Bulletin* by the GGD of Nijmegen [26].

In early August 2009, the regional GGDs were alerted to the fact that student and university faculty associations were getting ready to welcome students for the new academic year. The LCI advised the regional GGDs to discuss the necessary procedures with these associations. For example, they should be aware of how to recognize people with possible infection in an early stage of the illness, should know who would carry out diagnostic testing and which measures had to be taken for confirmed cases [C, July 24, 2009]. To this end, in collaboration with the RACers, the LCI distributed a document that could be used by the regional GGDs when they were advising student and faculty associations about how to act. At the same time, the standard recommendations in the document 'Large public events during the 2009 H1N1 influenza pandemic' were revised [C, August 7, 2009].

Due to the increase in the number of cases of 2009 H1N1 flu, from July 30, 2009 onwards, the regional GGDs were no longer required to register all suspect cases in Osiris. On this point, it would be enough for the regional GGDs to report just the laboratory-confirmed cases and any epidemiologically-linked close contacts who met the criteria of the case definition; these would then be registered in Osiris as a possible case. If the patient concerned came from abroad, then this fact had to be recorded in the field reserved for comments [C, July 30, 2009].

In late July 2009, it became clear that in day-to-day practice there was sometimes a lack of clarity relating to the period in which a person was infectious, and therefore also the period relating to home isolation. For this reason, in an Inf@ct message sent on July 30, 2009, the LCI repeated the prevailing policy that had been partly based on the OMT recommendations. A patient was considered to be infectious from the onset of symptoms (first day of illness) up to and including the seventh day of illness or until the patient had shown clinical recovery. The level of infectivity was at its highest at the beginning of the illness. This meant that a patient who, for example, had completely recovered after 4 days of illness, was no longer infectious and therefore did not need to stay at home any longer [C, July 30, 2009].

On August 5, 2009, the fourth OMT meeting was held, followed by a meeting of the BAO on August 6, 2009. The BAO voted in favour of all the OMT's recommendations and handed them over to the Minister of Health, Welfare and Sport [H, August 6, 2009]. Based on the advice from the OMT and the BAO, the Minister of VWS then announced the following decisions regarding the pandemic on August 6, 2009: From August 6, 2009, laboratory diagnostics would only be indicated for:

- patients who were admitted to hospital on suspicion of infection with the 2009 H1N1 pandemic virus;

or

- patients not admitted to hospital who had a possible infection with the 2009 H1N1 pandemic virus and who had exceptional clinical indications e.g., pregnant women in their third trimester and for patients who were extremely ill.

The compulsory notification for individual cases of confirmed 2009 H1N1 pandemic flu was dropped. Only cases of laboratory-confirmed infection with influenza A or the new 2009 H1N1 pandemic virus in patients admitted to hospital and/or those who had died were subject to compulsory notification. The 2009 H1N1 pandemic virus

remained notifiable as a group A notifiable disease. Both the treating doctor and the microbiologist involved were obliged to comply with this compulsory notification and could consult with the GGD if necessary. The changes in compulsory notification were implemented on August 15, 2009. Confirmed cases of 2009 H1N1 pandemic flu that had been established in psychiatric institutions did not have to be reported because these people were not being admitted as a result of infection with the 2009 H1N1 virus. But patients did have to be registered if they died as a result of the 2009 H1N1 pandemic virus. Verenso (an organization supporting geriatric specialists) also adapted its guideline for preventing the spread of influenza in nursing homes and care homes in accordance with the new policy [C, August 14, 2009; G, August 5, 2009].

The case definitions for probable and confirmed cases were amended by the CIb on August 15, 2009 [C, August 7, 2009].

- Probable case: Laboratory confirmation of a case of infection with an influenza A virus in a person who has been admitted to hospital on the grounds of the severity of the clinical symptoms and/or has died either in hospital or elsewhere.
- Confirmed case: Laboratory confirmation of a case of infection with the 2009 H1N1 pandemic influenza virus in a person who has been admitted to hospital on the grounds of severity of the clinical symptoms and/or has died either in hospital or elsewhere.

In order to keep track of the total number of patients in the Netherlands with clinical signs of infection with the 2009 H1N1 virus, the OMT felt that the number of CMR monitoring stations should be extended in the very short term (1 to 2 weeks). The OMT recommended taking extra measures for financial incentives to rapidly increase the level of GP acceptance regarding participation in the monitoring stations and to encourage them to pick up the proposals for enlargement that had been put forward [G, August 5, 2009].

The fourth OMT meeting recommended that antiviral drugs should be given to people in risk groups from August 7, 2009 onwards. This decision was based on the advice from the clinical working party under the leadership of Professor JT van Dissel. The recommendation from the working party named the risk groups that would be eligible for treatment with antiviral drugs [G, August 5, 2009]. These risk groups were specified in a schematic framework that was sent to general practitioners in a letter from the CIb. The letter from the CIb was sent via Inf@ct on August 7, 2009 to all doctors registered under the Individual Healthcare Professions Act [*Wet BIG*] in the Netherlands [C, August 7, 2009]. Such antiviral therapy for risk groups helped to limit any developing drug resistance and prevented overtreatment [G, August 5, 2009]. There were no further indications for the prophylactic use of antiviral drugs. The CIb strongly advised against giving a supply of antiviral agents to worried citizens as this could lead to incorrect use of the drugs and to resistance [C, August 7, 2009].

The advice from the clinical working party under the leadership of Professor JT van Dissel was an important addition to the fourth OMT meeting. This was mainly because from that point onwards, the clear message being conveyed to the rest of the world was that the 2009 H1N1 flu was relatively mild in nature. The recommendations relating to treatment policy during the pandemic were approved by the fourth OMT meeting (August 5, 2009) with one minor adjustment relating to the possible treatment of pregnant women in the first and second trimester. As the experience with neuraminidase inhibitors in pregnant women was limited, an increased risk for the unborn child in this period could not be ruled out with any certainty. For this reason, pregnant women in the first and second trimester could not be included in the treatment group. At an individual level, however, a treating doctor could decide – based on his own professional judgement and in consultation with the patient – to give oseltamivir treatment in the first two trimesters of pregnancy.

After the fourth OMT meeting, the document, whose title is translated as: 'Guideline for preventing infection in hospitals during the 2009 H1N1 pandemic' was drawn up by an expert commission under the leadership of Professor JAJW Kluytmans. This practical guideline described the actions that needed to be taken within the framework of infection prevention. These were intended for use by local policy-makers and contained recommendations that were formulated as concretely as possible but just needed to be adapted to the local situation. The underlying principles of the guideline consisted on the one hand of an optimal protection of hospital staff and patients and was, on the other hand a measure to ensure sufficient staff deployability [G, August 5, 2009].

During the OMT meeting of August 5, 2009, the capacity of ICUs in the Netherlands was discussed. In July 2009, a memorandum was written by a CIb working party under the leadership of the EPI relating to the capacity of ICUs; the title of the memorandum translates as follows: 'Demand for hospital beds and beds on the ICU during the peak of an influenza pandemic' (July 23, 2009). This was presented to the Ministry of Health, Welfare and Sport, the relevant professional groups, the NVZ and the Dutch Federation of University Medical Centres (NFU). Various model-based calculations were made as to the expected number of ICU admissions; these took various assumptions on the progression of the 2009 H1N1 pandemic as their starting point. During the fourth OMT meeting, there was a discussion on the uncertainties relating to the shortage of ICU beds. According to the OMT, a great deal of attention was being paid at hospital level and by the professional groups involved to preparations for the eventuality of a shortage of ICU beds. However, it was not clear who was responsible at national level for the coordination and the consequences of any shortage of ICU beds that might occur. The OMT advised the BAO to request the NVZ to prepare for a shortage of ICU beds and to ask for advice on how to deal with such a situation. In addition, the OMT advised the BAO to discuss the coordination of bed shortage scenarios with hospitals and to ensure that – at national level – there was always daily up-to-date information regarding the number of ICU beds available in the Netherlands [G, August 5, 2009].

The possible closure of schools was also discussed during the fourth OMT meeting. Based on epidemiological evidence, it was clear that young adults around 18 years of age were playing the biggest role in the spread of influenza. Based both on the limited data that was available and on empirical material relating to the 1918 pandemic in the US, the OMT concluded that there were now arguments in favour of closing schools. However, such a measure would result in extensive logistical problems that could not be overseen by the OMT at that point in time. Therefore, school closures were not recommended by the OMT for the time being. This would have been a valuable measure to employ had there been more information available

at the time on the vaccine supply and delivery situation. Some time could most probably have been gained through the closure of schools – for example, the peak of the pandemic might have been delayed – and this might also have brought about a reduction of the burden put on hospitals. The EPI produced a memorandum on this subject that was presented to the Ministry of VWS; the title translates as: 'School closures during an influenza pandemic'. The Ministry of VWS was advised by the OMT to bring the logistical and social problems associated with school closures into focus [G, August 5, 2009].

On August 7, 2009, all pharmacies including those maintained by GPs and hospitals were supplied with courses of oseltamivir in sachets containing 75 mg; these supplies were drawn from the national store. GPs could prescribe this drug to patients (but only on indication) who could then obtain it from the pharmacy free of charge. Pharmacies could, however, charge a prescription fee. Subsequently, patients would have to make up the suspension themselves according to the instructions in the patient leaflet. Because antiviral drugs were now going to be used on a large scale, it was absolutely essential that any side effects be reported through the Dutch Pharmacovigilance Centre (Lareb) [C, August 7, 2009]. Now that the delivery of oseltamivir had been handed over to the mainstream channels, the LCI reported via Inf@ct on August 14, 2009, that supplies to the regional GGDs would be discontinued. However, the supplies that the regional GGDs still held did not need to be returned [C, August 14, 2009].

On August 14, 2009, the NHG advised GPs not to treat patients with an influenza-like illness with antiviral drugs just as a precautionary measure. At the time, the percentage of 2009 H1N1 flu-positive samples from the CMR monitoring stations was around 10%. This meant that indiscriminately treating people who were not in a risk group would lead to overtreatment. However, should a patient meet the epidemiological description of the 2009 H1N1 pandemic virus or have severe underlying conditions, then the NHG did advise treatment with oseltamivir. After consultation with the CIb, this tenet was included in the triage guideline for GPs [C, August 14, 2009].

6.4 Government communications

6.4.1 International

On June 24, 2009, the ECDC indicated in its situation report that they had organized press conferences so that journalists could ask questions about the 2009 H1N1 pandemic and they could convey the latest information on the pandemic. These press conferences were broadcast as live webcasts via the ECDC website [B, June 24, 2009].

In the WHO's weekly epidemiological report (WER) of June 26, 2009, recommendations were given on the measures surrounding surveillance and control that were based on the knowledge available at the time. This took into account the large differences in the epidemiological situations between countries [B, June 26, 2009].

On June 27, 2009, the ECDC indicated that they were neither responsible for developing clinical guidelines nor for validating specific national guidelines relating to the 2009 H1N1 pandemic. In its situation report, the ECDC referred to the 'swine flu clinical package' that had been developed by the Department of Health in the United Kingdom. This information could be used by health care workers during a pandemic situation when there was increasing demand for clinical care. The ECDC reported that the information was specifically designed to work within the structure of the health

care system as it existed in the UK and could probably not be used in other European countries [B, June 27, 2009].

In its situation report of June 29, 2009, the ECDC presented an overview of the WHO recommendations and guidelines relating to pandemic preparedness and response. On this point, referrals were also made to reports of WHO meetings on the 2009 H1N1 pandemic [B, June 29, 2009].

On June 30, 2009, the ECDC communicated a risk assessment for the two cases of 2009 H1N1 pandemic flu in Denmark that were resistant to oseltamivir. The conclusion was drawn that the two mutations did not pose any risk to public health and the ECDC's expectation was that resistance would now occur more frequently [B, June 30, 2009].

From early July 2009, the WHO stopped giving daily pandemic updates. Only exceptional figures were reported with the 'normal' figures being conveyed on a weekly basis [E, July 10, 2009]. In mid July 2009, the WHO surveillance procedure was revised and countries were now asked to report the number of H1N1 flu-related deaths to the WHO on a weekly basis [E, July 18, 2009].

On July 3, 2009, the ECDC distributed the link to the guidelines from the UK's Department of Health on the practical implementation of the mitigation ('treatment') strategy in the UK [B, July 3, 2009].

On July 5, 2009, the EU Member States were asked via the EWRS if they wanted to hold a teleconference in order to gain insight into which countries were in the containment phase and which were in the mitigation phase. Only a very few Member States responded to this request [E, July 6, 2009].

Around July 9, 2009, the WHO published a check list for clinical patient care that was intended for hospital staff who were dealing with suspected cases of 2009 H1N1 pandemic flu. The WHO's check list encompassed both the clinical management of individual patients and general control measures for communicable diseases [B, July 9, 2009].

On July 10, 2009, the WHO changed the nomenclature for the pandemic flu virus again: the new name was: Pandemic (H1N1) 2009 [B, July 10, 2009]. In the Netherlands, the Ministry of Health, Welfare and Sport and RIVM-com decided not to change the nomenclature [C, July 10, 2009].

From July 11, 2009, the ECDC situation reports incorporated the cases in Aruba and the Dutch Antilles under the figures for the Netherlands [B, July 11, 2009].

From July 17, 2009, onwards, the WHO no longer published the table containing the data for confirmed cases worldwide. The WHO asked each country to report on the number of cases each week insofar as this was possible. Those countries that had transmission within the population were asked to report the indicators – these were comparable to the activity indicators that had been drawn up for the seasonal influenza. Documents on the surveillance of the 2009 H1N1 pandemic were available on the WHO's website [B, July 17, 2009].

On July 20, 2009, the ECDC published a revision of their risk assessment for the 2009 H1N1 pandemic. The EPI ensured that a summary of this was uploaded to the CIb website with an explanation in Dutch. According to the ECDC, the 2009 H1N1 pandemic virus would continue to spread further in Europe and the substantial

uncertainty relating to the virus would continue. The ECDC also said that most of the people infected with the 2009 H1N1 virus in the US and Europe had shown only mild clinical symptoms. However, much remained unclear surrounding the pandemic, given that transmission in Europe was still too limited to be able to assess the effects. From indications from Europe and North America, it was evident that there were significant differences in the severity of both the pandemic flu and the seasonal flu. The new virus was appearing particularly in adults under the age of 60 years who also had a chronic disease (this included people with severe obesity), pregnant women and very young children [B, July 20, 2009].

From July 24, 2009, the CDC no longer reported all the confirmed and possible cases of 2009 H1N1 pandemic flu. The CDC appreciated that such data represented only a small portion of the actual number of cases. Therefore, the CDC reported only the total number of hospital admissions and deaths that resulted directly from the virus. The normal surveillance systems were used to follow the progression of the outbreak of 2009 H1N1 pandemic flu. The surveillance updates were posted on the FluView website at regular intervals [B, July 26, 2009].

On July 31, 2009, the ECDC published a report containing analyses of individual cases; this data had been collated by EU countries. This ECDC report stated that transmission within a population was taking place in 27 EU countries and 3 EFTA countries and that transmission between countries was frequent. The age group that was affected the most was that of people under the age of 20 years. People over the age of 60 years were affected less often but were admitted to hospital more frequently. The shift of policy to mitigation had had negative consequences for the surveillance of individual cases in nearly half of the reporting countries [B, July 31, 2009].

The ECDC stopped presenting the data for individual cases from August 11, 2009. From that date onwards, the ECDC communicated only the data relating to mortality, hospital admissions and any ICU admissions. The name ‘situation report’ was changed to ‘daily update’. The reporting of new cases outside Europe was discontinued because many countries had stopped reporting their total figures. This meant that the figures that were reported were no longer representative of the actual situation. Only the figures for the number of deaths that resulted from the 2009 H1N1 pandemic virus were still reported for countries outside Europe [B, August 11, 2009; E, August 11, 2009].

Every Thursday, from August 13, 2009, the ECDC published a special section on the evolution of the 2009 H1N1 pandemic virus in selected countries outside Europe. The objective of this was to provide any interested parties with easily accessible information on the trends associated with the 2009 H1N1 pandemic [B, August 13, 2009].

6.4.2 National

In late June 2009, the LCI was receiving many telephone calls from the regional GGDs who said that they had serious doubts about carrying out the OMT’s recommendations. Many of the regional GGDs thought that it was an illusion to think that the introduction of the virus to the Netherlands could be kept at bay through the intensive tracing of infected people. The regional GGDs were asked by the LCI (via Inf@ct) to report all clusters as far as it possible so that sustained transmission in the Netherlands could be demonstrated to the OMT. More information on virus transmission in the Netherlands would lead to changes in the policy employed [C, June 24, 2009]. On June 25, 2009, the regional GGDs were once again (via Inf@ct)

asked to show understanding for the measures that had been advised by the OMT. For this purpose, the LCI pointed out in the same Inf@ct message that exceptions to the rule relating to policies in place were always possible in a certain patient or contact or in a given situation, as long as such decisions were based on professional judgement and responsibility. Further, the LCI could always be approached for advice if this was needed [C, June 25, 2009].

On June 30, 2009, through Inf@ct, the LCI distributed a standard letter for general practitioners that had been written by the LCI and the NHG. This letter addressed the role of GPs during pandemic alert phase 6. The regional GGDs were requested to circulate this letter to all GPs in their region [C, June 29, 2009]. The standard letter was also uploaded to the NHG and RIVM websites on June 30, 2009 [C, June 30, 2009].

On July 3, 2009, via Labinf@ct, a letter was distributed from the respective chairmen of the NVMM and the working party for Public Health Care and Infectious Diseases (WOGIZ). In this letter, laboratories in the Netherlands were informed of the 2009 H1N1 pandemic situation and the policy deployed [D, July 3, 2009].

On July 4, 2009, by request, the EPI gave a presentation about the model for the 2009 H1N1 pandemic (modelling pandemic Influenza A (H1N1)) during a WHO meeting held in Geneva.

Around July 22, 2009, the FAQs (including those for diagnostics) for GPs were distributed via the regional GGDs and the NHG website. The FAQs were compiled in consultation with COM, the regular MMLs, NVMM, LCI and EMC [D, July 22, 2009].

On July 30, 2009, the LCI used an Inf@ct message to distribute the recommendations for funeral directors; this had been compiled by the regional GGD of The Hague. The LCI also uploaded these recommendations to the CIb website. Information on the opening of the new helpline number (0800-1100) for all queries from the general public concerning the 2009 H1N1 flu pandemic was also announced in the same Inf@ct message. The regional GGDs could also refer companies with queries to this number. The helpline fell under the Postbus 51 information service with the general number (0800-8051) remaining open. The new number was put on the VWS website and also communicated by RIVM-com through the CIB website [C, July 30, 2009].

From late July 2009, all questions relating to the vaccine and the vaccination campaign that reached the RIVM-com and the CIb departments were referred to the NVI and the Ministry of VWS [E, July 28, 2009].

From August 4, 2009, the special CIb website for 2009 H1N1 pandemic flu was amended by the RIVM-com. From that date onwards, anybody consulting the website could choose between public information or information for professionals. This meant that the information could be presented in a much clearer format [C, August 7, 2009]. Information on the number of hospital admissions and underlying conditions was also uploaded to the website from August 4, 2009 onwards [E, August 7, 2009].

On August 7, 2009, the regional GGDs were asked to circulate the CIb letter that contained the detailed explanation of the OMT/BAO recommendations to the general practitioners and after-hours medical posts in their region. The CIb also sent the letter, which contained information on the compulsory notification and advice relating to antiviral drugs, to all BIG-registered doctors and it was also distributed via Inf@ct [C, August 7, 2009]. The advice from Professor JT Dissel’s working party, the title of

which translates as: 'Use of neuraminidase inhibitors in the 2009 H1N1 virus pandemic' was uploaded to the CIb website on August 10, 2009. This advice was changed slightly on August 12, 2009; for example, the treatment advice for HIV-infected people and for people with reduced resistance was set out more clearly. The CIb encouraged the regional GGDs to consult this source whenever necessary [C, August 7, 2009].

In the fourth OMT meeting held on August 5, 2009 the CIb recommended that the standard framework for the prevention of infection in hospitals during the pandemic – which had been compiled by a commission of experts under the leadership of Professor JAJW Kluytmans – should be conveyed to the NFU and the NVZ. In addition, the CIb was advised to approach Verenso and ask them to revise the Verenso guideline 'Influenza in nursing homes' and bring it into line with the standard framework [G, August 5, 2009].

On August 7, 2009, RIVM-com organized a second CIb update meeting for the press. This update session was chaired by Professor RA Coutinho, who is director of the CIb. The speakers at this meeting included Professor JT van Dissel, doctor A Timen and a representative from the NVZ. During this CIb update session, the new policy for diagnostics, notification and treatment of the 2009 H1N1 flu was explained in more detail. It was also pointed out that the figures on the CIb website for the number of cases was about to be changed because of the adjustments made regarding compulsory notification [G, August 5, 2009]. In the CIb press update session, the message conveyed to the public was that the 2009 H1N1 influenza illness was mild.

Because the summer holiday period was almost over, the LCI thought it advisable to bring schools and child care facilities up to date. For this reason, the LCI communicated (via Inf@ct) a sample letter and an information guideline for child care facilities on August 14, 2009. The emphasis in the policy was mainly on following hygiene rules, and encouraging children, teachers, and group leaders with symptoms fitting those of influenza to stay at home. The LCI was aware of the difficulties facing a school or child care facility if they had to inform all the parents of a class of children whenever a cluster or suspected cluster of the 2009 H1N1 pandemic virus was discovered. Parents could also be asked to read the public information leaflet produced by the Ministry of VWS and, if their child showed any signs of flu to contact their GP. In order to monitor any clusters of pandemic flu occurring in schools and child care facilities in the region, the sample letter contained a proposal that schools and child care facilities should notify the GGD if more than one third of the children in a particular class was ill at the same time. On August 17, 2009, via Inf@ct, a new version of the information material was distributed because the rules for compulsory notification had not been properly outlined. The same Inf@ct message included as an attachment, comparable information for schools which had been included as a section of the procedures manual *Health risks in primary schools and out-of-school childcare facilities*. This information had been revised at the request of the regional GGDs. To keep the information as consistent as possible, all documents were amended on the following point: if any child became ill, then the GP should be consulted whenever this was deemed necessary [C, August 17, 2009].

On August 14, 2009, the guideline on the 2009 H1N1 flu pandemic was uploaded to the CIb website under the tab 'Infectious diseases A-Z'. For the duration of the pandemic alert phase, this guideline replaced both the initial influenza guideline and the procedures manual *Part 2 Incidental Introduction of a New Human Influenza Virus in the Netherlands*. Where necessary, the guideline contained references to relevant information elsewhere on the CIb website or on third party websites. The document was regularly revised in accordance with the ongoing developments and

advancing insights into the H1N1 virus. At the same time, a Factsheet for the 2009 H1N1 pandemic flu (known internally at the CIb as an ISI for Infectious Diseases) was developed that could be used by the regional GGDs in their public information campaign; the FAQs were amended in accordance with the new policy [C, August 7, 2009; C, August 14, 2009].

Due to a lot of pressure from the media, a weekly CIb press conference was organized by RIVM-com on Fridays from August 14, 2009 onwards. These press conferences always started with an overview of the current state of affairs, that was based on the most up-to-date surveillance data, after which one or more themes were put under the spotlight.

6.5 Meetings

6.5.1 International

From July 1-3, 2009, on the initiative of the Mexican government, a meeting of the Health Ministers from 43 countries was held in Cancun; the objective of this meeting was to evaluate the 2009 H1N1 pandemic situation and to exchange information and experiences relating to the international response. The experiences from countries heavily affected by the 2009 H1N1 flu virus were presented and an epidemiological update was given [B, July 9, 2009].

On July 2 and 3, 2009, the Swedish president of the EU organized a meeting of experts for the Member States to discuss the pandemic influenza preparedness plans, the lessons that had been learned and the steps that still needed to be taken. The WHO and the European Commission also participated in this meeting alongside the EU countries [B, July 6, 2009]. The discussions focused on how collaborative efforts could improve pandemic preparations by analyzing and sharing past experiences. The follow-up step to this meeting was a meeting of the European Council of Ministers held on July 6-7, 2009 to discuss – along with other issues – their experiences with the 2009 H1N1 influenza pandemic. The ministers were shown presentations by the ECDC and the EMEA. Furthermore, the ministers were addressed via a video link by Dr. Margaret Chan who was the DG of the WHO [B, July 7, 2009]. The most important principal conclusions from both of the above meetings were published in the ECDC situation report dated July 11, 2009, [B, July 11, 2009].

A teleconference with the ECDC and the WHO was organized for July 20, 2009, by the DG-SANCO. During this session, the main focus was on the vaccine for the 2009 H1N1 virus [E, July 21, 2009].

6.5.2 National

On June 29, 2009, the CIb organized a meeting for the regional GGDs and the GHOR assistance services to discuss the new influenza virus. In this meeting, the latest state of affairs surrounding the 2009 H1N1 pandemic was discussed. The roles of the GGD and the GHOR during a pandemic at alert phase 6 were also discussed. In the Inf@ct message sent on July 22, 2009, the LCI said that a clinical working party chaired by Professor JT van Dissel had compiled a draft advisory report 'Use of neuraminidase inhibitors in the 2009 H1N1 virus pandemic'; this had been requested by the CIb. This draft report was presented for comments to the Consultation Group for Infection and Immunity of the Health Council of the Netherlands. The core issue in this advisory report related to whether or not every citizen of the Netherlands with an influenza-like illness should be treated with neuraminidase inhibitors in the event of a manifest pandemic. The question here was whether it would be better – considering the relatively mild disease symptoms of the 2009 H1N1 virus – to aim treatment specifically at high-risk patients in groups that would be further defined.

The clinical experts in the working party advised the following: aim treatment at high-risk patients. The advice of the working party was presented to the fourth OMT meeting that was planned for August 5, 2009 [C, July 22, 2009].

In the Inf@ct message sent on July 22, 2009, the LCI said that a commission of experts, under the leadership of Professor JAJW Kluytmans and under the responsibility of the WIP was drawing up a guideline for the prevention of 2009 H1N1 virus infection and for prophylactic treatment in hospitals [C, July 22, 2009].

On July 28, 2009, a meeting was held with the RACers, representatives of the NHG and the LHV. During this meeting, the proposal – put forward by the RACers – for a monitoring system to keep an eye on the work pressure in primary care was discussed. This resulted from the general expectation that the workload for GPs that was associated with the 2009 H1N1 pandemic virus would only increase from August onwards. There was an expectation that many patients would consult their GP practice and that it was quite possible that GPs would be temporarily unable to work because they would become ill with the flu themselves. This would lead to primary care coming under pressure in some places. The RACers had pointed out in July 2009 that in many places very little had been arranged to monitor the continuity of GP care during the pandemic's peak. The RACers were therefore taking their own initiative to develop a monitoring system. This plan was discussed with all those involved during the meeting of July 28, 2009. The possibilities for an upscaling operation at local level were also discussed in this meeting. The most important outcome from the meeting was that GPs concluded that, as a professional group, they were themselves primarily responsible for the continuity of GP care and for monitoring that continuity. The GPs voted in favour of reporting to the GHOR at municipal level. The RACers' report of this meeting was communicated via Inf@ct on August 7, 2009 [C, August 7, 2009].

The fourth OMT meeting was held on August 5, 2009. Among other matters discussed at this OMT meeting were the advice given by Professor van Dissel's clinical working party, the guideline for the prevention of infection in hospitals, drawn up by the expert commission led by Professor Kluytmans, and the EPI's memorandum concerning the capacity of ICUs [G, August 5, 2009]. On August 6, 2009, the BAO voted in favour of all the OMT's recommendations and handed them over to the Minister of Health, Welfare and Sport [H, August 6, 2009].

6.6 Vaccination policy for the 2009 H1N1 virus

6.6.1 International

On July 7, 2009, the WHO's most important advisory body, the Strategic Advisory Group of Experts (SAGE) on Immunization presented its initial advice on vaccination in relation to the 2009 H1N1 pandemic situation. According to SAGE, the essential health care infrastructure had to be preserved by means of immunizing employees who worked in the health care sector. In addition, recommendations were made with regard to the priority groups for vaccination against H1N1 influenza. Based on the situation at the time as well as the information that was available, SAGE assumed that 2 doses of pandemic vaccine were needed to effectively protect an individual against the 2009 H1N1 virus [A, July 7, 2009]. In addition, SAGE said that there was no need to consider changing the production of vaccine from that of seasonal influenza to pandemic influenza since the production of the vaccine for seasonal influenza (2009-2010) was almost complete. SAGE explained that this would not therefore, present any problems with regard to the production of the pandemic vaccine. SAGE further recommended promoting the production and the use of adjuvants and live weakened influenza vaccines, because of the possible limited

amount of vaccine that was available worldwide. Full background information on the SAGE meeting could be found on the WHO website [B, July 14, 2009].

Around July 22, 2009, clinical trials on the 2009 H1N1 pandemic vaccine were commenced in Australia and China [B, July 22, 2009].

On July 28, 2009, comments were added to the ECDC website concerning the WHO's vaccine study which had been published in the journal *Vaccine* [27]. According to the ECDC, the worldwide capacity for the production of seasonal and pandemic vaccine had increased considerably since the WHO's publication on June 27, 2009 [B, July 28, 2009].

On August 6, 2009, the WHO published on its website a document on the safety of pandemic vaccines and the vaccine production process [B, August 6, 2009].

6.6.2 National

On July 10, 2009, via Inf@ct, the message was conveyed that it was still not clear whether or not all citizens in the Netherlands would be vaccinated and in which order this would take place. It was also pointed out in the same Inf@ct message that occupational health doctors still had a lot of questions about the policies for dealing with the 2009 H1N1 pandemic [C, July 10, 2009].

The Inf@ct message sent on July 22, 2009 stated that the Ministry of VWS had established working parties to handle the preparations needed for the 2009 H1N1 pandemic vaccination campaign in the Netherlands [C, July 22, 2009]. A steering committee was set up in order to substantively advise the Minister of Health, Welfare and Sport about the proposed vaccination strategy and the infrastructural sustainability of policy for vaccinating all or part of the population of the Netherlands against the 2009 H1N1 pandemic virus. This steering committee included representatives of the following bodies: Ministry of VWS, NVI, CIb, CvB, LHV, NHG, GGD NL, Lareb and GHOR NL. From July 15, 2009 onwards, the steering committee met once a fortnight and discussed any vaccine-related information known up to that date, the members were requested to provide advice about any questions that had remained unanswered up to that point to the extent that they applied to the up-to-date situation [28]. The steering committee gave advice on the major vaccination issues, such as the prioritizing of vaccinations (in the event that the vaccine supply were to be staggered) interferences, contraindications and the registration of adverse reactions [C, July 22, 2009]. After the vaccination campaign, this steering committee was also to function as a consultative group, advising the supervisory committee on the evaluation of the approach taken in regard to the 2009 H1N1 pandemic.

From July 15, 2009 onwards, a weekly meeting of the coordinating action team was held. The task of the coordinating action team could be described as follows: to deliver substantive contributions from the perspective of an individual's responsibility with regard to the two main areas of logistics and communication [28]. The coordinating action team was concerned, for instance, with the preparations needed for a possible massive vaccination campaign which intended to vaccinate the entire population in the Netherlands. In addition, three other scenarios were specified: vaccination of the people in medical risk groups, vaccination of health care sector staff and vaccination of people in various specific age groups. The intention here was to determine the exact procedure for all four scenarios and work out who had to perform which task and when this had to be done. The Health Council would recommend whether or not vaccinations would be carried out and, if the answer was yes, who would be eligible. The final decision lay with the Ministry of Health, Welfare

and Sport but, because of the time constraints, waiting for an operational vaccination strategy to be written was not realistic. For this reason, all plausible scenarios were described. The CIb, CvB, NVI, RCP, Lareb, NHG, LHV, National Influenza Prevention Programme (SNPG), the umbrella organization for occupational health and reintegration (Boaborea), regional GGDs, GHOR and other medical advisors took part in this working party. Input for the working party was also provided by the steering committee.

On July 24, 2009, it became clear that the pandemic vaccine would probably be supplied later than October 2009 [E, July 24, 2009].

On July 31, 2009, the RIVM reported via a newsletter compiled by RIVM-com, that the vaccination for the 2009 H1N1 virus had resulted in changes being made to the HPV vaccination campaign. The RIVM said that the vaccination of 12-year-old girls against cervical cancer was being held off until the spring of 2010. This had been decided by the Ministry of VWS after consultation with the RIVM and GGD NL. The reason for this postponement was the developments around the 2009 H1N1 pandemic and the expected burden that would be put on the regional GGDs with regard to the control of the new virus. Many organizations were involved both in controlling the flu and in the HPV vaccination campaign. The implementation of the HPV vaccination and the control of the flu virus was complex and could possibly lead to logistical and organizational problems if the number of people with the 2009 H1N1 flu virus increased. The vaccination of 12-year-old girls for cervical cancer was to have started in September 2009. Those girls between the ages of 13-16 years who had started their HPV vaccination programme before the 2009 summer holiday could complete their course of 3 jabs.

During the fourth OMT meeting of August 5, 2009, the current situation regarding the mass vaccination campaign was discussed. During the meeting, it was announced that the CIb, in collaboration with the Health Council, was going to organize a meeting on August 10, 2009 in order to discuss the prioritizing of groups eligible for vaccination. The resulting joint recommendations had to be handed in to the Ministry of VWS in the third week of August. The main focus of discussions was that of the unknown adverse reactions of the vaccine because a new adjuvant was being used in its production. In addition, the combination of the seasonal flu vaccination with the new H1N1 flu vaccine was being investigated. On the date of the fourth OMT meeting, the exact delivery date of the pandemic vaccine was still not clear [G, August 5, 2009].

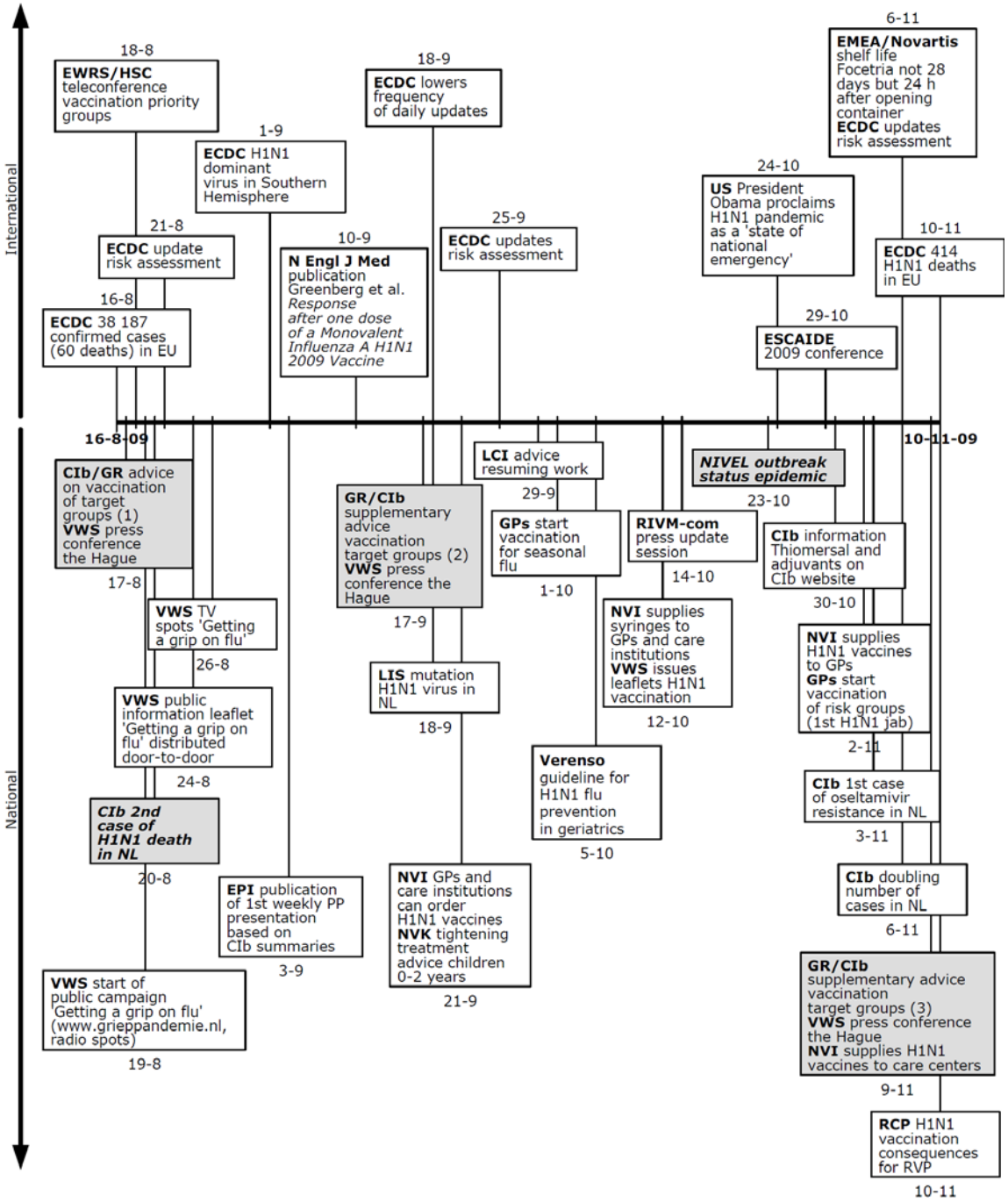

Figure 6 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period August 16, 2009 to November 10, 2009.

7 Period 5: from August 16, 2009 to November 10, 2009

The outbreak of 2009 H1N1 virus reaches pandemic proportions in the Netherlands and the vaccination campaign is started
In the Netherlands, the fifth period of the pandemic was characterized by large-scale spread of the 2009 H1N1 pandemic virus. The outbreak of the 2009 H1N1 influenza virus was officially declared an epidemic in the Netherlands on October 23, 2009. During this same period, the vaccination campaign for the 2009 H1N1 pandemic virus was started and three advice documents were issued about the selection of target groups for vaccination.

7.1 Situation

7.1.1 International

On August 16, 2009, there were a total of 38,187 confirmed cases of 2009 H1N1 pandemic flu in EU and EFTA countries and of these, 60 had died as a result of their infection. At that point in time, some 2024 people outside Europe had died as a result of the new influenza virus. The 2009 H1N1 pandemic continued to spread further all over the world. Within the space of just 1 week, the first confirmed cases were reported in the Democratic Republic of the Congo, Cameroon, Madagascar, East Timor and Zambia. Moreover, a large number of countries reported the first deaths resulting from the virus [B, August 16, 2009].

In Australia, by August 20, 2009, there had been 32,799 confirmed cases of 2009 H1N1 flu infection reported, which included 128 deaths. At the time, there were 455 people in Australia still in hospital because of an infection with pandemic flu and 95 of these had been admitted to an intensive care unit. The total number of hospital admissions in Australia since the proclamation of the 2009 H1N1 pandemic virus was 3802. At the time, there were 3086 confirmed cases in New Zealand, of which 951 were admitted to hospital with 233 diagnosed as having pneumonia. In 38 of the confirmed cases in New Zealand an acute respiratory distress syndrome (ARDS) had been diagnosed. Up until then, there had been 15 deaths resulting from infection with the 2009 H1N1 pandemic virus [B, August 20, 2009].

By August 22, 2009, 27 EU countries and 3 EFTA countries had reported cases of infection with the 2009 H1N1 pandemic virus; the total number of confirmed cases since April 2009 amounted to 42,099 and included 80 deaths. Most of the cases being reported around this time were in Germany and the United Kingdom. The majority of hospital admissions reported at the time were in the United Kingdom. Outside the European Union, 2459 deaths resulting from the new virus had been reported to the ECDC. The number of cases worldwide was estimated at 250,595 [B, August 22, 2009].

As the seasonal influenza began in the Southern Hemisphere, the influenza type that was predominant in that part of the world was the 2009 H1N1 pandemic flu virus. On September 10, 2009, the ECDC released information on the situation in Australia. There had been a total of 165 deaths in Australia resulting from infection with the 2009 H1N1 pandemic virus. At that point in time, there were still 335 people ill with flu in hospital and 64 (19.1%) of these were being nursed on an ICU. Up to September 10, 2009, the total number of hospital admissions in Australia was 4610. The national data for Australia showed that there had been a clear decrease in the number of cases appearing in the previous couple of weeks. Moreover, in most areas

of Australia clinical surveillance showed that the peak of the initial pandemic wave was over [B, September 10, 2009].

On September 18, 2009, there were only 3 countries in Europe (Ireland, Sweden and the UK) that had reported influenza-like activities above the baseline. From the total number of sentinel samples that tested positive for influenza, 96% were found to be of the 2009 H1N1 pandemic flu type [B, September 18, 2009].

On October 2, 2009, the CDC reported that 99% of all influenza A viruses for which subtyping was taking place, were of the 2009 H1N1 pandemic variant. Of all the samples tested, 99.7% were for influenza type A and 0.3% for influenza B [B, October 6, 2009].

On October 24, 2009, the USA's President Obama proclaimed a 'state of national emergency' relating to the 2009 H1N1 pandemic [E, October 27, 2009]. This announcement made it easier for health authorities in the US to carry out their work.

On October 23, 2009, the WHO announced that worldwide more than 414,000 laboratory-confirmed cases of 2009 H1N1 pandemic flu had been reported to the WHO, which included nearly 5000 deaths. According to the WHO, this was a serious underestimation of the number of actual cases, because many countries had stopped counting the numbers of individual cases. The WHO said that the number of people made ill by the H1N1 pandemic virus in the tropics was on the decline [B, October 26, 2009].

In early November 2009, there was an increase in influenza activity reported in Europe. In the Ukraine, there was a lot of unrest due to a sharp increase in respiratory infections in the population [E, November 3, 2009]. Later on it became clear that the situation in the Ukraine had been caused by the 2009 H1N1 pandemic virus. However, no mutations were found in that country [E, November 20, 2009].

On November 9, 2009, the ECDC published an account of the continuing spread and increase in the number of 2009 H1N1 pandemic cases in Europe in its 'Weekly Influenza Surveillance Overview' (WISO). There was evidence of increased pandemic activity in 15 of the 20 countries that reported on flu trends. Four of these countries (Austria, Estonia, Portugal and Romania) reported an increase in influenza activity within their borders for the first time [B, November 9, 2009]. By November 10, 2009, the ECDC had reported 414 fatal cases of 2009 H1N1 infection in EU and EFTA countries. Outside Europe, 6094 people were reported by the ECDC as having died from an infection with the 2009 H1N1 virus.

7.1.2 National

On August 20, 2009, a second patient died in the Netherlands from infection with the 2009 H1N1 pandemic virus. As had been the case for others, this patient also had underlying conditions. In the Netherlands, in that same week 10 people were admitted to hospital due to an influenza infection. Up to that point, there had only been 46 people admitted to hospital because of flu in the Netherlands.

On September 18, 2009, the EPI reported seven cases of Severe Acute Respiratory Infection (SARI) to the ECDC as well as four more deaths resulting from infection with the 2009 H1N1 pandemic virus in the Netherlands.

Around September 18, 2009, the LIS detected a mutation in a virus sample from a patient infected with the 2009 H1N1 pandemic virus – this was confirmed

retrospectively as the patient was already ill. In other influenza virus types, the mutation was associated with higher virulence. At the time, however, it was unclear whether this mutation would also lead to more severe clinical symptoms in the infected patient [E, September 18, 2009]. A second person was found to have the same mutation on September 22, 2009 [E, September 22, 2009].

By mid October 2009, the LCI had been informed of confirmed clusters of the virus occurring in schools and child care facilities in various regions of the Netherlands. In general, infections caused by the 2009 H1N1 pandemic virus were mild and people recovered within a few days. However, the attack rate was often found to be high. On October 16, 2009, the GGD of Rotterdam Rijnmond reported on a cluster of 2009 H1N1 pandemic virus in a residential facility for children with multiple disabilities. An 8-year-old child (the index case) at a small-scale residential facility for children with multiple disabilities was admitted to hospital with fever (39 °C), vomiting, impending dehydration and increasing need for oxygen supplementation. Three days following admission, the diagnosis of 2009 H1N1 pandemic flu was confirmed. In the residential facility where 7 children were living at the time, 3 other children had clinical symptoms. Two of them had high fever and vomiting and 1 of them subsequently developed a runny nose without fever. The third child had an influenza-like clinical picture. None of the children living in this facility had diarrhoea. A total of 5 children were found to be infected with the 2009 H1N1 pandemic virus. None of the staff members at the facility tested positive but 1 employee had been ill and the other 2 had mild symptoms. The index patient recovered completely following admission to hospital for 8 days. The other 4 children with relatively mild symptoms recovered within 1 to 4 days. From the cluster in the region of GGD Rotterdam Rijnmond, it was clear that the course of the illness caused by the 2009 H1N1 virus was not always typical, i.e. with fever and respiratory symptoms. This meant that it was also important to check any children with underlying conditions who presented atypical signs of illness for the 2009 H1N1 pandemic virus [C, October 16, 2009].

In the Netherlands, the 2009 H1N1 pandemic virus acquired the official status of epidemic on October 23, 2009. This resulted from data from the CMR monitoring stations, where for 2 weeks in a row, more than 5.1 patients per 10,000 inhabitants had been found to have an influenza-like illness.

In the week of October 30, 2009, 4 people with confirmed 2009 H1N1 infection died in the Netherlands. Three of these cases – a 56-year-old woman, an 11-year-old girl, and a 6-year-old boy, had underlying conditions; the fourth case was a 25-year-old man from another European country whose previous medical history was unknown. In the same week, a great deal of media attention was paid to the death of a 16-year-old girl due to a fulminating illness. However, no infection with the 2009 H1N1 pandemic virus was confirmed in this patient. The LCI said that this case illustrated how important it was for the regional GGDs to always consider other pathogens as the cause of illness, even when the clinical evidence pointed to a probable diagnosis of 2009 H1N1 flu infection [C, October 30, 2009]. An increase in the number of hospital admissions was also reported by the CIb during this week. A total of 131 cases of 2009 H1N1 flu infection were admitted to hospital in the Netherlands within the space of 1 week, these included 9 pregnant women [E, October 29, 2009].

By the end of October 2009, the number of people with influenza-like symptoms reported to the CMR monitoring stations was rising sharply. According to the CIb, the pandemic wave had certainly started in the Netherlands. This was confirmed by a rapid increase in hospital admissions and clusters occurring in schools. The CIb

expected the pandemic peak to be reached within a few weeks [D, November 10, 2009].

On November 3, 2009, the CIb reported the first patient in the Netherlands who was infected with an H1N1 virus that was resistant to oseltamivir. The virus was found in a patient with sustained symptoms following treatment with oseltamivir. On November 10, 2009, a total of 40 patients had been reported worldwide (from Europe, North and South America and Asia) with a virus resistant to oseltamivir, and in most cases resistance had developed during treatment with the drug. The LIS said that this was not entirely unexpected. Moreover, the LIS said that such viruses were less able to spread autonomously. Resistance was possible in patients who were being treated but who did not recover well and also in patients who continued to have a high viral load after 5 days of treatment [D, November 10, 2009].

On November 6, 2009, the CIb reported that the number of reported hospital admissions in the Netherlands had doubled compared with the previous week. In a news report compiled by RIVM-com, the CIb stated that the number of people who were consulting their GPs due to flu-like symptoms had increased. Based on this information, the CIb determined that the Netherlands was in the grip of a mild influenza epidemic.

On November 10, 2009, a total of 744 patients were admitted to hospital in the Netherlands due to infection with the 2009 H1N1 pandemic virus. This number rose each day by 30 to 40 people. Around November 10, 2009, 12 patients with an infection of the new virus were admitted to an ICU [E, November 10, 2009]. In week 46 of 2009, the total number of hospital admissions in the Netherlands rose to 909. In that same week, the CIb reported that 22 people had died in the Netherlands as a result of H1N1 pandemic flu infection.

7.2 Diagnostics

7.2.1 International

On August 17, 2009, in its MMWR, the CDC published information on the development of oseltamivir resistance in two patients who were not linked to each other but who did both have severe immune suppression. The article emphasized the need for monitoring any developing resistance to antiviral drugs in patients with immune suppression [29].

7.2.2 National

On August 19, 2009, information was circulated via Labinf@ct about the sensitivity of the BinaxNOW® rapid test for detecting the 2009 H1N1 pandemic virus. The specificity of this test was found to be less than optimal. Considering the importance of a correct and reliable diagnosis for the new virus, the LIS said that it would not be wise to rely on the results obtained through the BinaxNOW® antigen test – even when the results were positive [D, August 19, 2009].

Extensive influenza surveillance from August 15, 2009

The regular influenza surveillance was continued as usual during the 2009 H1N1 pandemic. This surveillance consisted of that conducted at the CMR monitoring stations in collaboration with the NIVEL and the SNIV, the subtyping of influenza viruses by the NIC at EMC, and the monitoring of resistance to antiviral agents. In addition, more extensive surveillance was carried out. The data from the extra surveillance was used, for instance, for the CIb's weekly summaries, the expert meetings for disease detection and those of the response team. Below you will find a summary of the content of this extensive surveillance:

Weekly mortality monitoring
As well as the information on mortality rates reported in the CIb weekly summaries, as from August 6, 2009, the EPI also received a weekly dataset from Statistics Netherlands (CBS) covering all registered deaths and including the causes of death since January 2009. This enabled to calculate excess mortality rate for each week, due to the reporting delay. The extensive summary of mortality rates (all causes) was distributed internally at the CIb.

Hospital admissions and mortality rates (source: GGD-Osiris)
After the rules for compulsory notification were changed on August 15, 2009, surveillance took place for patients admitted to hospital and/or those who had died as a result of an infection with the 2009 H1N1 pandemic virus. The number of hospital admissions, ICU admission and deaths was monitored by the EPI on a weekly basis. Other information was also recorded, such as, the patients' characteristics, the age distribution, gender distribution, geographical region, underlying conditions and pregnancy.

Admission to Paediatric ICUs (PICUs)
The eight university medical centres in the Netherlands all have a paediatric intensive care unit (PICU). In the period from September 9, 2009 to December 12, 2009, the PICUs reported the number of new patients that had been admitted to the unit in the previous week for each age group to the CIb on a weekly basis. They also reported the number of beds that were occupied by cases of 2009 H1N1 pandemic influenza – this was done at a set time each week. The eight PICUs were given aggregated feedback from the EPI on the notifications that had been made in the previous week. This was a summary of the following data:

- the number of children admitted to PICUs in the previous week and for the entire period;
- the percentage of beds occupied by influenza patients for the total available bed capacity per week.

Virology laboratories surveillance (source: Lab-Osiris and virology weekly bulletins)
Each week during the period from July 10, 2009 to April 26, 2010, the nine outbreak assistance laboratories in the Netherlands reported weekly the number of samples that they had tested and the number that had tested positive for the 2009 H1N1 pandemic virus. A differentiation was made with regard to the origin of the samples – from the GGDs, from patients admitted to hospital and those from elsewhere.

In the period September 14, 2009 to April 26, 2010, there was also an extra questionnaire added to Lab-Osiris which related to the age distribution of patients with 2009 H1N1 influenza who had been reported in the virological weekly bulletins. This meant that when 2009 H1N1 pandemic viruses were included in the virological weekly bulletins there was also the option of filling out this extra questionnaire. The questionnaire included questions on the age distribution of positive patients whereby a differentiation was made between samples from general practitioners/outpatient departments, hospital admissions, ICU admissions or patients who had died.

Issuing of oseltamivir (source: Foundation for Pharmaceutical Statistics (SFK)
From October 21, 2009 to May 25, 2010, the SFK reported to the CIb the number of doses of oseltamivir prescribed per week in the Netherlands.

Prevention of influenza symptoms in the Dutch population (source: Big Influenza Survey)
The Big Influenza Survey was set up in the 2003/2004 season and was a private initiative to document the incidence of influenza in the general public. Participants in the Big Influenza Survey were asked on intake to fill out a questionnaire that contained questions on demographic, medical and lifestyle aspects. During the influenza season (which – for the pandemic – was the entire year) the participants received a weekly e-mail containing a link to a

questionnaire on clinical symptoms – including influenza-like symptoms – which they might have developed since last visiting the site (www.grotegriepmeting.nl). If symptoms were indeed reported, then extra questions were posed with regard to GP consultation and any limitations experienced in daily activities as a direct result of the symptoms.

In the period October 28, 2009 to May 20, 2010, the Big Influenza Survey was a source of data, with regard to flu-like symptoms among its participants, for the CIb. This data contained information on the weekly incidence of influenza-like illness and the weekly incidence of various common cold and influenza-like symptoms. Information was provided on the number of people who had taken part in the relevant week and the age distribution of the participants. Also reported was information on the number of people with an influenza-like illness who did and did not consult their GP; this data was classified per age group.

On September 14, 2009, the first round of the 'Serosurvey for 2009 H1N1 pandemic flu' was conducted under the leadership of the EPI. During the first round of this study, approximately 3000 letters were sent to people selected at random from the Dutch population asking for their participation.

Serosurvey for the 2009 H1N1 virus
Serosurvey for the 2009 H1N1 pandemic influenza virus: this was a study conducted under the leadership of EPI into the age-specific infection attack rates of the virus in the Dutch population. Also investigated were the possible protective effects of a previous infection with seasonal influenza (H1N1, H3N2) and vaccination for preventing an infection and illness with the 2009 pandemic virus. The core objective of this study was to improve the model predictions for the progression of influenza epidemics (age-specific attack rates, expected duration of an epidemic and the expected effect of interventions such as vaccination, antiviral agents, and school closures). It was expected that the results of this project would help with the development of vaccination strategies for the future, for example, with such issues as which groups of people definitely need to be vaccinated, and which groups specifically do *not* need to be vaccinated. What is the best order for vaccination? How long prior to the influenza season should vaccination take place?

Serosurvey Method
This study used a repetitive cross-sectional study with age stratification. During the first round (September 14, 2009) approximately 3000 questionnaires were sent to randomly selected people in the Dutch population and during the second round (starting on March 21, 2010) approximately 10,000 questionnaires were sent. The subjects who filled out the questionnaires were subsequently asked to donate blood samples.

Memorandum with preliminary results of serosurvey
On August 25, 2010, the memorandum 'Age-specific infection attack rates of 2009 H1N1 pandemic influenza in the influenza season of 2009-2010' was drawn up by the EPI and sent to the Ministry of Health, Welfare and Sport. This memorandum was compiled on the basis of the preliminary results of the serosurvey study.

In the Labinf@ct messages sent on November 10, 2009, the LIS said that they were receiving signs that some laboratories were no longer able to cope with the demand for diagnostic testing and needed advice on how to prioritize. According to the LIS, GPs were probably now performing more diagnostic tests because of the reports in the media. At the time, the surveillance at the CMR monitoring stations showed that about half of the people who had been tested within the previous two weeks for flu-like symptoms, were indeed found to have the 2009 H1N1 pandemic virus. The CIb did not recommend performing diagnostic tests on people who did not have an

increased risk and who were recovering at home. Diagnostic tests were recommended for the following people:

- people whose symptoms were such that they had to receive treatment with antiviral agents. As previously mentioned, the antiviral therapy had to be started for these patients without first waiting for the results of the diagnostic tests;
- people with symptoms who were in a risk group, e.g. pregnant women, neonates and people with severe immune disorders;
- people admitted to hospital with respiratory infections;
- people who had been treated and had not made a good recovery.

It was clear from the surveillance from the CMR monitoring stations that at the time, only the 2009 H1N1 influenza virus was being diagnosed. According to the LIS, any additional diagnostic testing and/or subtyping of influenza A-positive samples was not really necessary. However, it did remain essential to consider good differential diagnostics, particularly because of the circulation of respiratory synctial virus (RSV) [D, November 10, 2009].

In early November 2009, the CIb was still concerned that changes to the 2009 H1N1 pandemic virus might occur, leading it to become more virulent or resistant. For this reason, from April 2009, random samples of viruses were partially sequenced, in collaboration with the OALs, in order to detect any mutations that might occur. For this purpose, other laboratories could also forward material to the LIS. The LIS wanted to at least receive virus-positive material from patients who were seriously ill or who had died. A few weeks previously, the EMC had already issued a protocol for a rapid test for an important mutation that had been found in viruses resistant to oseltamivir. Laboratories in the Netherlands could request rapid sequencing by telephoning the LIS and the EMC, which were working in collaboration with the regional GGDs and the LCI. Any urgent requests had to be sent direct to the LIS [D, November 10, 2009].

It was reported in the Inf@ct and Labinf@ct messages sent on November 10, that serological diagnostic testing for the 2009 H1N1 virus was not yet possible. Many people, but primarily pregnant women who were being offered vaccination for the 2009 H1N1 virus, wanted to know whether or not they had had the disease in the past. If that had been the case, then they would no longer have the vaccination. In principle, such testing via hemagglutination inhibition tests and microneutralization was possible, but these methods were not yet embedded into routine laboratory testing. For this reason, the LCI and the LIS advised the people concerned to have the vaccine anyway (probably an unnecessary measure) if the diagnosis was not confirmed through PCR during the illness; this was because previous infection with the virus in the past could not be presumed. Pre-vaccination tests were not recommended due to the limited diagnostic capacity available [C, November 10, 2009; D, November 10, 2009].

7.3 Control

7.3.1 International

In late August 2009, the WHO published guidelines on its website about the use of antiviral agents in patients infected with the 2009 H1N1 pandemic virus. These guidelines had been drawn up by an international panel of experts who had studied the literature available at that time with regard to the safety and effectiveness of these antiviral agents. Emphasis was placed on the fact that the use of oseltamivir and zanamivir could prevent severe illness and death from occurring, and could reduce both the number of hospital admissions needed and the length of stay in hospital. Using these antivirals could also help to slow down transmission of the

virus. According to the WHO, any decision on whether or not to treat a patient with antiviral agents had to be based on a clinical assessment and on what was known about the spread of the virus in the local population. In the guidelines, the WHO also indicated which groups of patients should be treated with which antiviral agent in any particular situation. Due to varying situations, the WHO guidelines could not be used in all countries across the globe, but they did serve to clarify the underlying arguments for antiviral use so that national governments could be helped with producing their own guidelines. In the Netherlands, the WHO guidelines did not lead to any changes being made to the policy already in place [B, August 22, 2009; B, August 26, 2009].

7.3.2 National

On September 21, 2009, the treatment advice for children under the age of 2 years was refined and distributed to all those involved by the Dutch Society of Paediatrics (NVK) via an Inf@ct message. This treatment refinement concerned children under the age of 2 years who met the case definition criteria but who neither had an indication for admission to hospital nor belonged to a medical risk group. If these children developed only mild disease symptoms, then diagnostic tests and treatment for the 2009 H1N1 flu virus were not considered necessary. If they had moderate disease symptoms, then there was an indication for H1N1 diagnostic testing and the doctor needed to consider whether treatment should be started whilst waiting for the test results to come back. Children who were seriously ill should, of course, be admitted to hospital [C, September 21, 2009].

On September 21, 2009, a memorandum from the infection committee of the Netherlands Society of Physicians for Persons with Intellectual Disabilities (NVAVG) was also distributed via Inf@ct. This memorandum set out recommendations with regard to the diagnostics, reporting and treatment of 2009 H1N1 pandemic flu. The memorandum did not address the measures required should an outbreak of 2009 H1N1 pandemic flu occur in an institution [C, September 21, 2009].

On September 29, 2009, the LCI distributed its recommendation 'Advice on resuming work following infection with the 2009 H1N1 pandemic virus'; this was also done via Inf@ct. This recommendation was supplementary to the standard guidelines for the prevention of infection in hospitals during the H1N1 influenza pandemic. As there was little evidence-based data available at the time regarding the infectious period, it was impossible to provide a definite indication of the number of days after which employees were no longer contagious. The CIb thought it plausible that the infectivity of a patient would decrease as the fever subsided. Therefore, the decision was taken to allow employees, both those in the health care sector as well as others, to return to work as soon as the fever had subsided; careful hand hygiene and cough etiquette measures would still need to be taken, however. Good hygiene measures helped prevent (as far as possible) the transmission of the virus by people who were possibly still infectious; this message completely corroborated the publicity campaign being conducted by the Ministry of VWS. Measures were only more vigorous for those employees who were working with vulnerable patients. These employees were only allowed to return to work 10 days after the symptoms had started or earlier if they had had a control RT-PCR test; if the employer requested the person to return to work (to avoid loss of care continuity), then protective measures had to be taken on the part of the employee. This advice was distributed by the WIP, the NCvB and the CIb to care institutions, occupational physicians and general practitioners. The information was also uploaded to the public information site of the Ministry of VWS [C, September 29, 2009].

On October 5, 2009 the standard guideline, translated as 'Prevention of and approach to the 2009 H1N1 influenza virus in geriatric medicine', which had been drawn up by Verenso was distributed via an Inf@ct message. The guideline was an addition to the existing Verenso guideline 'Prevention of the spread of influenza in nursing homes and care homes'. Verenso emphasized the importance of vaccination, both for seasonal influenza and for the 2009 H1N1 pandemic virus, for both the residents and the employees of homes. Diagnostics were essential if an outbreak of influenza was suspected in a home. If the 2009 H1N1 pandemic virus was confirmed, then the home could take the decision – just as with cases of seasonal influenza – to offer oseltamivir as prophylactic treatment to both residents and staff in order to curb the outbreak. With regard to the above, there was a preference for prophylactic treatment to be given in a research setting. For this purpose, the CIb had set up a randomized control trial in collaboration with Verenso and GGD NL. The new guideline was also uploaded to the Verenso website (www.verenso.nl) [C, October 5, 2009].

On October 5, 2009, the doses of oseltamivir for children under the age of 12 months were changed by the CIb. There was still little experience with administering oseltamivir to children under the age of 6 months [30, 31]. However, new data seemed to point to the fact that very young children developed relatively high levels of the drug in their blood when they had been given doses of 3 mg/kg twice daily. Therefore, the treatment advice was amended:

- children younger than 1 month: 2 mg/kg body weight twice daily;
- children between the ages of 1 month and 3 months: 2.5 mg/kg body weight twice daily;
- children between the ages of 3 months and 12 months: 3 mg/kg body weight twice daily.

Hospital admission was indicated for children under the age of 3 months [C, October 5, 2009].

On November 10, 2009, a hygiene guideline was distributed by the LCI via Inf@ct in order to prevent the spread of the 2009 H1N1 pandemic virus among clients and employees working with the learning disabled as far as this was possible. Clear recommendations regarding hygiene – which were based on three scenarios – were given. The guideline was compiled by the infection committee of the NVAGV as a supplement to the memorandum on diagnostics and treatment, which had been distributed on September 21, 2009 [C, November 10, 2009].

According to the LCI, from November 10, 2009 onwards, diagnostic tests for the 2009 H1N1 pandemic virus in schools were no longer always necessary. Where a cluster of flu-like symptoms developed at a school in the Netherlands during an evolving epidemic, it could be presumed that the 2009 H1N1 pandemic would be found to be the cause. In situations where the 2009 H1N1 virus had already been confirmed in a few schools in a particular region, through laboratory tests, then the likelihood that the virus was circulating was so high that testing other children for the virus – in schools where clusters were also occurring – would not be of any added value [C, November 10, 2009].

7.4 Government communications

7.4.1 International

On August 21, 2009, the ECDC published public health care information on the use of antiviral agents during an influenza pandemic; this information related specifically to the 2009 H1N1 pandemic. The same material could also be found on the ECDC

website [B, August 21, 2009]. On August 22, 2009, the ECDC's risk assessment was updated and published on their website [B, August 22, 2009].

On September 14, 2009, the ECDC revised the recommended assumptions for pandemic preparations in EU countries, this was the document entitled 'ECDC guidance on public health measures'. The reason for this was based on information from the EU country that had been affected the most: the United Kingdom. The assumptions for July 2009 were lowered and for the first time an estimate was given for the number of ICU beds that might be needed for each country affected by the pandemic [B, September 16, 2009]. On September 15, 2009, the ECDC published the first Weekly Influenza Surveillance Overview.

From September 18, 2009, no more daily updates were produced by the ECDC during the weekend [B, September 18, 2009]. From September 29, 2009, the ECDC no longer reported the numbers of confirmed cases that had been reported by EU and EFTA countries. Because the rules for compulsory notification had changed in most countries, the numbers reported no longer presented a realistic picture of the current situation. The ECDC continued to monitor the progression of the pandemic both in and outside Europe by studying the mortality figures. On this point, the ECDC emphasized that the number of reported deaths per country was a gross underestimation of the actual number of deaths caused by the 2009 H1N1 pandemic. From September 18, 2009, the daily updates were published each weekday morning [B, September 29, 2009].

On September 25, 2009, based on new information that had become available, the ECDC revised its risk assessment. The underlying principles of the risk assessment were relaxed somewhat [B, September 28, 2009].

In early October, 2009, Google Flu Trends added 14 European countries to the programme. This programme estimated the influenza activity in a country in real-time on the basis of the number of times that a search had been made for issues connected with the 2009 H1N1 pandemic virus. Google Flu Trends covered a total of 20 countries worldwide [B, October 8, 2009]. Microsoft launched a 'web-based pandemic influenza self-assessment tool' on October 8, 2009.

On November 6, 2009, the ECDC's risk assessment was once more updated and published on their website [B, November 9, 2009]. It was clear from this document that while more children had been hospitalized with the H1N1 flu compared with seasonal influenza, the mortality rate in children infected with the new flu was no higher. The ECDC predicted that for a 'reasonable worst case scenario' 20% of the population would be affected by the 2009 H1N1 pandemic virus [E, November 10, 2009].

7.4.2 National

From August 15, 2009, the table with the number of confirmed cases in the Netherlands was removed from the CIb website because of changes made to the rules for compulsory notification. The figures were actually no longer reliable because not all individual cases were now being registered. The CIb's flu website section 'current state of affairs' showed the figures for the number of hospital admissions and for deaths.

On August 17, 2009, the Ministry of VWS organized a press conference in response to the vaccination advice document 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritizing' which had been written jointly by the CIb

and the Health Council (GR). Attendees at this press conference included the Minister of VWS and the director of the CIb.

On August 19, 2009, the VWS publicity campaign with the catch phrase 'Getting a grip on flu' was started. The objective of this campaign was to ensure that the general public were kept up-to-date with regard to the characteristics of the illness and the recommended treatment. The corresponding website www.grieppandemie.nl contained all kinds of public information such as incidence, recognition and treatment of the 2009 H1N1 pandemic flu virus. The CIb also placed the FAQs on this website. At this point in time, the special CIb flu website was redesigned by RIVM-com to be used by professionals, which meant that the general public could now consult the new VWS website if they had any questions on the flu pandemic. From August 19, 2009, the spots that alerted people to hygiene and other precautionary measures that needed to be taken were broadcast on the radio; these covered coughing/sneezing into paper tissues and hand washing, and warned people to stay at home if they thought they were developing flu [C, August 7, 2009; August 14, 2009]. On August 8, 2009, announcements about the H1N1 flu were placed in daily newspapers.

From August 24, 2009, a public information leaflet (what you should do, what you must do, what the government is doing) was distributed door-to-door in the Netherlands as part of the 'Getting a grip on flu' campaign. In addition, from August 24, 2009, banner ads were placed on internet pointing people to hygiene measures and the (flu pandemic) website. From August 26, 2009, the broadcasting of television spots was started. These also covered coughing/sneezing into paper tissues and hand washing, and warning people to stay at home if they thought they were developing flu [C, August 14, 2009].

From September 3, 2009, the EPI published a weekly PowerPoint presentation on the CIb website that contained information from the CIb weekly summaries. These presentations could be used by professionals when they had to make their own presentations. From that point onwards, the EPI also produced a supplement to the CIb weekly summaries that was used for the meetings of the response team (up to and including the last response team meeting on December 18, 2009). The supplement contained additional information on the following data:

- virology laboratories surveillance;
- raw data from the CMR monitoring stations (NIVEL);
- faw data from the SNIV surveillance;
- number of hospital admissions per GGD region;
- number of admissions to PICUs;
- number of hospital admissions, ICU admissions and deaths;
- age and gender distribution for hospital admissions, ICU admissions and deaths;
- number of pregnancies among patients admitted to hospital or on the ICU;
- vaccination status with regard to seasonal influenza vaccination and 2009 H1N1 pandemic vaccination among hospital admissions, ICU admission and deaths;
- reporting delay for notifications in Osiris;
- Google Flu Trends.

On September 17, 2009, the Ministry of VWS organized a press conference in response to the vaccination advice document, translated as 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritizing' which had been written jointly by the CIb and GR. This press conference was attended by, among others, the Minister of VWS and the director of the CIb.

On September 22, 2009, information was sent via an Inf@ct message on an influenza-like illness cluster among children and supervisors at a day nursery involving 24 cases of illness. The preliminary diagnosis of 2009 H1N1 virus infection was made and the necessary measures were taken. However, 3 samples tested negative; this meant that it was less likely that the 2009 H1N1 pandemic virus was the pathogen. The specific pathogen was never investigated but in the Inf@ct message, the regional GGD for The Hague indicated that other GGDs should, at that point in time, not make and communicate the diagnosis of infection with the 2009 H1N1 pandemic virus too quickly and that they should communicate with others [C, September 22, 2009].

From the end of September 2009, an overview of the policy for pregnant women was available for professionals on the CIb flu website. The policy for oseltamivir treatment and the vaccination policy for pregnant women had been laid out schematically and was also included in the LCI guideline on 2009 H1N1 pandemic influenza [C, September 29, 2009].

Since August 15, 2009, only patients who were admitted to hospital as a result of infection with the 2009 H1N1 pandemic virus were subject to compulsory notification. In early October 2009, it was evident that there was significant delay on the part of hospitals between the time when the diagnosis was made and the notification of the case in Osiris. Therefore, the LCI sent a message to the regional GGDs via Inf@ct requesting them to point out to hospitals the importance of reporting cases quickly [C, October 5, 2009].

On October 14, 2009, a third CIb update session for the press was organized by RIVM-com. During this meeting, the focus was mainly on the vaccine and the practical side of the vaccination campaign [E, October 6, 2009]. As well as CIb employees, this meeting was also attended by representatives of the LHV, the CBG and the Ministry of VWS.

On October 30, 2009, the LCI asked the regional GGDs – that might be confronted with deaths resulting from the H1N1 flu – to contact them because of the considerable impact that such a situation could have. The LCI subsequently ran through a check list in order to structure the collection of information. With this measure, the CIb hoped that news concerning any death resulting from the 2009 H1N1 pandemic virus would be uniformly structured [C, October 30, 2009].

In early November 2009, due to the amount of new and amended information on the 2009 H1N1 pandemic vaccination, RIVM-com made the CIb flu website more accessible with the addition of the tab ‘New information for professionals’. This enabled professionals to see at a glance which documents were new or had been amended [C, November 10, 2009].

On November 4, 2009, the communication tool kit for influenza and colds was uploaded to the RIVM website. This tool kit had been amended ahead of schedule because of the 2009 H1N1 pandemic.

On November 9, 2009, the Ministry of VWS organized a press conference in response to the vaccination advice document ‘Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritizing’ which had been written jointly by the CIb and the Health Council. This press conference was attended, among others, by the Minister of VWS and the director of the CIb.

Communication tool kit for influenza and colds
The LCI communication tool kits contained consistent and correct communication materials such as: documents, basic products, semi-finished products, photos, illustrations et cetera., intended for use by intermediaries such as communication professionals involved in health care – especially those at regional GGDs. Using such a tool kit enables everyone involved to use the same widely supported information. The communication tool kit for influenza and colds has existed since 2007 and contains general information on the prevention of influenza and colds. In October 2009, the overlapping messages were synchronized through the introduction of the campaign 'Getting a grip on flu' and the tool kit was enhanced.
The tool kit for Influenza and Colds was placed under the tab 'infectious diseases' on the RIVM Information Centre's website on November 4, 2009.

The communication tool kit for the campaign on the yearly influenza vaccination was also updated and improved by adding answers to the questions about the link between the yearly vaccine for seasonal influenza and the vaccine for the 2009 H1N1 virus.
At the same time, the materials from the 'Getting a grip on flu' campaign were uploaded to the RIVM Information Centre's website. This enabled posters, leaflets, radio and TV spots and banners to all be found at the same familiar locations.

7.5 Meetings

7.5.1 International

On October 12, 2009, the EU Ministers of Health gathered in Luxembourg for an extra meeting of the European Council to discuss the situation surrounding the 2009 H1N1 pandemic. Issues such as vaccination strategy and the availability of vaccines in the various EU countries were on the agenda [B, October 15, 2009].

The meeting of the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) was held on October 26, 2009. Employees from the EPI took part in this meeting.

7.5.2 National

On September 7, 2009, the CIb organized another meeting for the regional GGDs and the GHOR assistance services. The aim of this meeting was to inform participants about the up-to-date 2009 H1N1 pandemic situation in relation to the preparations for vaccination procedures manuals and the continuity of care.

On November 6, 2009, the regional GGDs met together in response to the joint advice from the CIb/GR committee to protect children aged 6 months to 4 years and members of their household against the 2009 H1N1 pandemic virus. All regional GGDs were represented at this meeting. Prior to this, other meetings had been held of the GGD NL, GHOR and RCP in which all kinds of issues – such as the 2-week vaccination plan and the number of vaccination locations – had been discussed. The points discussed in these earlier meetings were presented during the meeting of November 6, 2009. Due to the exceptional pandemic situation, it was agreed that all the regional GGDs would simultaneously offer vaccinations to the Dutch population in the weeks of November 23 and December 14, 2009; this would take place at 250 locations spread throughout the country. Subsequently, all the regional GGDs made preparations for carrying out the vaccination campaign within 2 weeks. During the preparation period, the GGD/GHOR NL also organized a meeting for the substantive experts on the medical aspects of the vaccination campaign. In addition, an evaluation meeting was organized between the first and second vaccination rounds [32].

7.6 Vaccination policy for the 2009 H1N1 virus

7.6.1 International

On August 22, 2009 the CDC published the recommendations from the Advisory Committee on Immunization Practices (ACIP) relating to the use of the monovalent 2009 H1N1 pandemic vaccine. The recommendations had been made on the basis of an article containing epidemiological and clinical data for determining which population groups should be vaccinated first. According to the CDC, the first approved vaccines could be expected in the US by mid October 2009. The ACIP recommended vaccinating as many people as possible and as quickly as possible. To this end, target groups for vaccination were defined [B, August 22, 2009].

On August 31, 2009, the ECDC published the policy viewpoint of the European Commission which reflected a collective European approach to identify target and priority groups for vaccination against the 2009 H1N1 pandemic virus [B, August 31, 2009].

On September 4, 2009 the vaccine manufacturer Novartis published the results of an initial clinical trial which had demonstrated that a single dose of vaccine (MF59 adjuvanted vaccine) would provide up to 80% protection against the H1N1 pandemic virus [B, September 4, 2009].

Around September 16, 2009, the intramuscular pandemic vaccines produced by CSL Limited, Novartis and Sanofi Pasteur, and the nasal spray vaccine by Medimmune were approved by the FDA. The Novartis, Sanofi and Medimmune vaccines were approved for both adults and children, while the CSL vaccine was only indicated for adults. According to the ECDC, clinical trials had shown that one dose (15 mg) would be sufficient to induce an immune response in adults but that 2 doses would be necessary for children [B, September 16, 2009].

China was the first country in the world to start a vaccination programme for 2009 H1N1 pandemic influenza; this was on September 22, 2009. The Chinese health authorities had the aim of vaccinating 65 million people – 5% of the total population in China – before the end of the year [B, September 22, 2009].

On September 29, 2009, the European Commission approved two pandemic vaccines based on advice given by the EMEA on September 24, 2009. The Focetria® (Novartis) and Pandemrix® (GlaxoSmithKline) vaccines were approved for use in all EU and EFTA countries. This also allowed vaccine manufacturers to add virus strains of the H1N1 pandemic virus to existing mock-up vaccines [B, September 30, 2009]. On October 2, 2009, the EMEA positively approved the pandemic vaccine Celvapan® (Baxter) [B, October 5, 2009].

On October 12, 2009, the European Commission also approved the use of the vaccine Celvapan® during the 2009 H1N1 pandemic.

On September 10, 2009, an article was published by Greenberg et al., *Response after one dose of a monovalent Influenza A (H1N1) 2009 Vaccine – preliminary report,* in which evidence was given that one dose of the vaccine provided sufficient protection and a second vaccination was therefore not necessary. However, the participants in this study had all been healthy people between the ages of 18 and 64 years which meant that the results could not be extrapolated to people with a medical indication or to children under the age of 18 years. The advice contained in the article could thus be interpreted to mean that it was only applicable to healthy people working in health care who were offered vaccination because of the nature of their work [33].

The Greenberg article led to many unanswered questions among the general public in the Netherlands and thus also affected GPs and the regional GGDs. On October 24, 2009 the EMEA confirmed the recommendations they had made in September 2009 relating to the number of vaccine doses per person. The EMEA studied the data from clinical studies for 3 authorized pandemic vaccines: Celvapan®, Focetria®, and Pandemrix®. From this, the EMEA concluded for the 3 vaccines that it was preferable to give 2 doses with a period of at least 3 weeks in between. The data on Pandemrix® and Focetria® that was available at that time indicated that 1 dose might be sufficient for adults. However, there was too little evidence available for the EMEA Commission to recommend a vaccination schedule of just a single dose [B, October 26, 2009].

On October 28, 2009, the advisory body of the WHO (SAGE) revised its vaccination advice given on July 7, 2009. The advice was changed to 1 dose of pandemic vaccine for people over the age of 10 years [A, October 28, 2009; B, November 2, 2009].

On November 5, 2009, the European document 'Benefit-risk strategy monitoring of Influenza A/H1N1 vaccines' was published by the ECDC and EMEA.

On November 9, 2009, the first FAQs on H1N1 vaccines for professionals were published by the ECDC on their website. On November 10, 2009, the first ECDC FAQs on H1N1 vaccines for the general public were published on the ECDC website.

7.6.2 National

On August 17, 2009, the CIb and the Health Council presented the vaccination advice document 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritization' to the Minister of VWS [I, August 17, 2009]. This advice recommended vaccination for the following risk groups:

- People with a medical risk corresponding to an indication for the yearly seasonal flu vaccination, therefore including all healthy people over the age of 60 years.
- Pregnant women in the medical risk group, but only those in the second and third trimester of pregnancy. The experts did not recommend vaccination for pregnant women who were not in a medical risk group.
- Staff working in the health care sector who might have had direct contact with patients from previously defined medical risk groups.
- Family members and carers of people with an extremely high risk of severe illness and death from influenza.

Vaccination of the entire population in the Netherlands was not recommended because the risk of complications from infection with the 2009 H1N1 pandemic virus seemed to be slender and information on vaccine side effects was not yet widely available. The Ministry of VWS took this advice completely on board. In the Inf@ct message of August 17, 2009, it was announced that the CIb/GR committee would meet once more in September 2009; the purpose of this meeting would be to reconsider broadening the vaccination indication (for children and adolescents) as and when more information on the vaccine characteristics and the patient population became available. Prioritizing within the specified groups was probably not necessary seeing as it was expected that the vaccine would be available in sufficient quantities. The complete CIb/GR Council advice was uploaded to the CIb flu website and several other sites [C, August 17, 2009].

On September 15, 2009, the *National procedures manual for vaccination of the 2009 H1N1 pandemic virus* with its accompanying appendices was published by the vaccination programme management team for the H1N1 pandemic virus under the

leadership of the 'Oude Gracht' management and consultation group. The procedures manual was a collective product of the steering committee and the coordinating action team. The objective of the manual was to describe the national framework and underlying principles needed for the implementation of the vaccination plan for the Dutch population against the 2009 H1N1 pandemic virus. In addition, the procedures manual acted as a guideline and to some extent provided protocols for the organization and implementation of the vaccination strategy. The procedures manual covered the following four separate scenarios:

- Scenario 1: Vaccination of medical risk groups.
- Scenario 2: Vaccination of people in age-related risk groups.
- Scenario 3: Vaccination of the entire population (mass vaccination).
- Scenario 4: Vaccination of medical professional groups.

Throughout the development of the vaccination campaign for the 2009 H1N1 pandemic virus and the safeguarding of its effective implementation, it was important from the national perspective to define a flexible vaccination strategy. This vaccination strategy encompassed the vaccination scenarios that, depending on how the target groups were prioritized – as set out in the advice from the Health Council – as on the virulence of the virus, could be specifically utilized to provide the best and most appropriate control of the virus. The national procedures manual was intended to act as a cornerstone for the uniform, effective and controlled implementation of vaccination for all those parties involved with the vaccination of parts or all the Dutch population [28].

On September 17, 2009, the CIb/GR committee issued an additional vaccination advice document for the 2009 H1N1 pandemic virus 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritization (2)'. Apart from the groups that had been specified in the advice of August 17, 2009, vaccinations were now also made available for pregnant women in the second and third trimester; these were carried out via primary care after consultation with the GP, midwife and/or gynaecologist. This group appeared to be at increased risk of severe illness as a result of the 2009 H1N1 pandemic virus. In the first trimester of pregnancy, however, there seemed to be a contraindication for pandemic flu vaccination, because experience with the vaccine was still limited and the foetus that was then at its most vulnerable. The CIB/GR committee did not see a vaccination indication for the other groups, such as healthy children. The document further advised that one vaccination was not sufficient to provide protection against the H1N1 virus (there was insufficient evidence of effectiveness in children and in risk groups) and that there had to be a period of at least 3 weeks between vaccinations. It was also recommended that the vaccination for seasonal influenza and the 2009 H1N1 pandemic influenza should not be given at the same time but with an interval of at least 2 weeks [I, September 17, 2009]. Again, this additional advice was uploaded to the CIb flu website [C, September 21, 2009].

Between September 21, 2009 and October 9, 2009, (weeks 39 to 41) general practitioners and care institutions could place their first orders for 2009 H1N1 pandemic vaccines from the NVI. Delivery of the H1N1 vaccines continued to depend on whether or not the vaccine manufacturers would deliver the vaccines on time. On the SNPG and the NHG websites there was a practical guide that could aid GPs, care institutions and regional GGDs to estimate how many vaccines they needed to order – this was based on the assessed risk for patients in the medical risk groups [34]. General practitioners ordered vaccines for their risk groups through the SNPG website. In mid August 2009, the Minister of VWS decided which health care institutions were eligible to order 2009 H1N1 pandemic vaccines for their staff. The

Minister of VWS decided that the H1N1 vaccine should be available for people working in the following health care settings:

- hospitals;
- ambulance services;
- general practitioners and after-hours medical post staff;
- nursing homes;
- care homes;
- institutions for the learning disabled;
- home care organizations;
- midwives.

Health care institutions could order the H1N1 vaccines directly through the NVI website. Subsequently, the institutions could then decide if they wanted to carry out the vaccination campaign within their own organization or hand this task over to others, e.g. the occupational health and safety service.

Ordering of 2009 H1N1 pandemic vaccines by general practitioners

Before GPs could order vaccines through the SNPG website, many issues still had to be resolved. For example, negotiations on the reimbursement for GPs per vaccination had to take place between the Ministry of VWS and the LHV. Consistent with its role in the yearly seasonal flu vaccinations, the Centre for Population Screening (CvB) took the initiative, together with the parties involved (SNPG, NVI, NHG and LHV), of ensuring that GPs could also vaccinate people in medical risk groups for the 2009 H1N1 pandemic virus. This was particularly relevant for the logistics, the web application for orders and the communication surrounding vaccines. In early July, 2009, the CvB put together an internal team to support the influenza vaccination programme coordinator. During the period from mid August 2009 to mid December 2009, the CvB took part in the meetings of the CIb's response team.

Web application

Prior to the 2009 H1N1 pandemic, GPs could order vaccines for seasonal influenza from the NVI by completing written order forms on paper. Around this time, work was being done on developing a web application so that the influenza vaccines could be ordered and declared electronically. During the 2009 H1N1 pandemic, the CvB arranged – in collaboration with the SNPG and the NVI – that the draft version of the web application be built at short notice so that it would be suitable for ordering the pandemic vaccines. The web application was available to GPs through the SNPG website.

Ordering based on 100% attendance rate of the target group

GPs and care institutions were advised when placing their first order, to base this on an attendance rate of 100% for the target group concerned and to subsequently order what they needed to complete the second round of H1N1 pandemic vaccinations.

Call centre

In collaboration with the NVI, the SNPG scaled up their help desk for GPs for the yearly seasonal flu vaccination into a call centre which was located at the NVI premises. GPs, and later on also care institutions, could contact the call centre with any queries relating to the 2009 H1N1 vaccination campaign. Internal agreements were made regarding who, i.e., call centre, LCI, NVI, or Postbus 51, would answer which type of questions; the LCI drew up a flowchart for this purpose. At the height of the vaccination period, the call centre was dealing with 1200 questions each day.

Vaccination registration
The CvB compiled a letter in consultation with the NHG which was signed by VWS and requested the designers of HIS (a registration system for GPs) to adapt their systems. They needed to allow GPs to register three vaccinations per patient per season instead of just one, and to note the date of vaccination as well as the batch number. This was because people in risk groups were eligible for the yearly seasonal flu vaccination and two doses of pandemic vaccination.

Public information leaflet: H1N1 vaccination for people in medical risk groups
After liaising with all parties involved, the CvB issued a public information leaflet relating to vaccination against the 2009 H1N1 pandemic virus for people in the medical risk groups. This leaflet was in addition to the standard public information leaflet on seasonal influenza. Finalizing the text, printing and distribution of the leaflet was organized by the Ministry of Health, Welfare and Sport and was an elaboration of the knowledge, experience and contacts of the National Influenza Prevention Programme (NPG). The design and weight of the leaflet were crucial factors for ensuring that GPs would send them to patients together with the letter of invitation for their flu vaccination.

Influenza vaccination take-up rate in medical risk groups
Each year, the CvB commissions the IQ Scientific Institute for Quality of Healthcare at Nijmegen to monitor the level of influenza vaccination take-up in medical risk groups (including healthy people over the age of 65 years) via the National Information Network for General Practice (LINH). In 2009, the CvB also requested IQ Healthcare to include the level of vaccination take-up for the 2009 H1N1 pandemic virus in medical risk groups (including healthy people over the age of 65 years). In addition, from November 2009, the CvB, together with the SNPG and RIVM-EMI, made weekly estimates of the preliminary level of vaccination take-up estimated for people in medical risk groups (including healthy people over the age of 60 years) and for health care sector staff. This was done through the web application for ordering vaccines, which also asked GPs and care institutions to indicate on a form (on a voluntary basis) how many people they had invited to be vaccinated and how many they had actually vaccinated.

Ordering of 2009 H1N1 pandemic vaccines by care institutions
Extensive preparations were also made before care institutions could order H1N1 vaccines from the NVI. For example, a coordinator for the vaccination of health care sector staff against the H1N1 virus was detached to the CvB from GGD NL; this was similar to the situation with the medical risk groups.

Web application and letter
The coordinator worked closely with the CvB to ensure, for example, that the web application for ordering the H1N1 vaccines would also be available to care institutions. Care institutions were given access to the web application through the NVI website. This web application was maintained by the SNPG. It was decided that the communication with the care organizations would be effected via the NVI website and not via the SNPG website. This step was taken to prevent any confusion arising in future in relation to the yearly seasonal flu vaccination occurring in future years. The coordinator for care institutions arranged for a letter – which was signed by the director of the RIVM – to be sent to care institutions that stated, along with other information, who should be vaccinated. To this end, at the request of the Ministry of VWS, the LCI compiled an overview of the kind of staff who were eligible for vaccination per care organization. The idea was that the employer himself had to make the final selection based on the clearest possible guidelines. The letter also explained the ordering procedure and communicated the information for logging on to the web application. Before the letter could be sent, a list of addresses had to be compiled which included all the institutions that needed to be informed about this issue – this task took some time to complete.

Registration of H1N1 vaccination by care institutions
For the registration of the vaccinations given by care institutions, the coordinator designed a registration form. This form could be accessed via the NVI website. Health care institutions were also free to make up their own registration method bearing in mind that it was important to include the following information: the name and date of birth of all people vaccinated, the type of vaccine given, the batch number and the date of vaccination. In addition, it was important that care institutions registered which vaccine and the batch numbers that had been used per location and per vaccination round [34].

From late September 2009, GPs were provided with supplies of the seasonal flu vaccine. From this point on, GPs started to vaccinate their patients against seasonal influenza. In a normal situation, GPs would be advised to give the yearly seasonal flu vaccination from mid October up to mid November – insofar as this was possible. This period offers optimum protection against both early and late waves of influenza. Because the seasonal flu vaccine was available earlier than the 2009 H1N1 pandemic vaccine, and because the vaccination against the 2009 H1N1 pandemic flu seemed to be more important than that for seasonal influenza, a meeting was organized by the CvB between the CIb and the NVI. During this meeting, it was decided that the NVI would distribute the vaccines for seasonal influenza as early as possible, although this largely depended on when the vaccines would be released. GPs were instructed by the SNPG, LHV and NHG to give the seasonal influenza vaccination in the month of October where possible, so that this round would be completed before the pandemic vaccines were supplied. This would enable the pandemic vaccination round to be administered as soon as possible. At the end of October 2009, it became clear that there was a small group of GPs who would be supplied with the seasonal flu vaccine and the pandemic vaccine with only a brief intervening interval. This group of GPs was approached separately by a letter from the SNPG and the LHV that said they could also choose to give the pandemic vaccine first if they preferred.

In practice it proved awkward to implement the advice from the CIb/GR 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritization' of August 17, 2009, that carers and household members should also be vaccinated. The CvB therefore consulted with the LHV, NHG and a few other specialist organizations on this point. Subsequently, on October 7, 2009, a letter was sent to professionals, including those at the LHV, and the professional associations for cardiologists, pulmonologists, gastroenterologists, nephrologists and oncologists; the letter, signed by the director of the CIb, outlined how the professional groups in question should handle this situation. The CvB also took the initiative of sending a letter to the LHV, Royal Dutch Organization of Midwives (KNOV) and the Dutch Society of Obstetrics and Gynaecology (NVOG) concerning the vaccination of pregnant women; the content had previously been discussed with the CIb. This letter (which was also signed by the director of the CIb) was sent on October 12, 2009.

The delivery schedules for the 2009 H1N1 pandemic vaccines changed frequently in this period – at least once a week – which made the planning of vaccination sessions very difficult. It was only in week 42 (October 12 to October 18, 2009) that it became clear when the vaccine manufacturers would deliver the first 2009 H1N1 pandemic vaccines to the NVI. The NVI received a pre-alert from the vaccine manufacturer during that week. In week 44 (October 26 to November 1, 2009) the pandemic vaccine was delivered to the NVI by the vaccine manufacturer. In the same week, GPs and care institutions received confirmation regarding their vaccine orders from the NVI.

Around October 30, 2009, information was published on the CIb website about Thiomersal (only in multi-dose containers) and the adjuvants in the pandemic vaccines was placed on the CIb flu website. There were concern and questions among medical professionals and the general public with regard to the use of these substances in the pandemic vaccines. In order to fulfil the need for information on this issue, the LCI uploaded a document to the CIb website *Thiomersal in vaccines, October 26, 2009*, with background information on the preservative. A similar document with information on the adjuvants was published on the site one week later. These documents explained the function of adding the substances to the vaccines and cited relevant data from the literature concerning safety issues [C, October 30, 2009].

On October 30, 2009, the LCI announced that the regional GGDs were receiving many phone calls from GPs asking whether or not people who had had the flu in the second half of 2009 should still be vaccinated. The LCI said that there was no point in vaccinating people for whom infection with the 2009 H1N1 pandemic virus had been confirmed by diagnostic testing. However, for those people who had symptoms of flu but had not undergone diagnostic testing, vaccination was still recommended by the CIb [C, October 30, 2009].

In late October, 2009, a special information leaflet on the vaccination was compiled by the Ministry of VWS, the CIb and the CvB for women in the second and third trimester of pregnancy. An information leaflet was also compiled for staff working in the health care sector who were eligible for vaccination. The text was based on the existing leaflet for the medical risk groups. Both leaflets were uploaded to the website www.grieppandemie.nl [October 30, 2009].

Instructions for the preparation and administration of the pandemic vaccine were published by the NVI and the LCI on the CIb flu website (instruction sheet for preparing Pandemrix® and for Focetria® October 30, 2009). As well as these instruction sheets, the LCI also uploaded background information on the vaccination campaign and the vaccines to the CIb website; this was intended for professionals who were involved in carrying out the campaign [C, October 30, 2009].

In weeks 42 and 43 (October 12 to October 19, 2009) the NVI supplied the syringes (1 ml fixed needle syringes) to general practitioners and care institutions. After consultation with the NVI and the SNPG, the CvB arranged for min/max thermometers to be sent to general practitioners and care institutions to draw attention to and facilitate the monitoring of the cold chain.

In week 45, (November 2 to November 8, 2009) the packs of pandemic H1N1 vaccine (multi-dose Focetria®) was supplied by the NVI to general practitioners in the Netherlands. This meant that GPs could start vaccinating people in risk groups from November 2, 2009, which was the official start of the vaccination campaign in the Netherlands. GPs used various GP information systems to call up patients and register the vaccinations administered. GPs were supported in their tasks surrounding the 2009 H1N1 pandemic vaccination for the people in risk groups mainly by the SNPG, CvB, NHG, LHV and the NVI. In week 46, (November 9, 2009 to November 15, 2009) the packs of pandemic vaccine (multi-dose Focetria®) were delivered to care institutions in the Netherlands.

The registration of all adverse reactions resulting from the 2009 H1N1 pandemic vaccine was carried out at the Dutch Pharmacovigilance Centre, Lareb. Reports of acute adverse reactions relating to the 2009 H1N1 pandemic vaccination in pregnant

women (second and third trimester) were dealt with by the Teratolgy Information Service.

The responsibility for the vaccination of the populations in the Dutch Antilles and Aruba was placed with the government of those countries [28].

On November 9, 2009, the joint CIb/GR committee once more issued supplementary advice on 2009 H1N1 pandemic vaccination. In the advice document, 'Vaccination against 2009 H1N1 pandemic influenza: target groups and prioritizing (3)', the CIb/GR committee recommended that children under the age of 5 years should be protected against the 2009 H1N1 flu virus. As well as tackling morbidity and mortality in this age group, the expectation was that protecting these children from the virus would prevent hospital admissions and thereby alleviate capacity problems in the paediatric intensive care units (PICUs). This advice led to young children aged from 6 months to 4 years being offered vaccination. For babies under the age of 6 months – for whom no vaccine had been registered – vaccination of other members of the household or similar contacts was recommended [I, November 9, 2009]. The EPI compiled the memorandum translated as: 'Risks of 2009 H1N1 pandemic infection in children and adolescents' for the collective CIB/GR committee.

Paediatric intensive care units (PICU)
The 8 Dutch university medical centres (UMCs) at Leiden, Nijmegen, Amsterdam (2x), Utrecht, Maastricht, Groningen, and Rotterdam all have a special intensive care unit for babies and children (PICU). The total capacity of the 8 PICUs is 107 beds. In order to have some kind of insight into the ICU capacity required for the 2009 H1N1 pandemic, these PICUs reported at a set time each week the number of patients that had been admitted during that week as a result of infection with the pandemic virus. At the same time, they reported the number of beds that were occupied at that point in time by patients with a 2009 H1N1 influenza infection. The age group was recorded for all admitted patients. The number of beds occupied by pandemic flu patients each week could be charted as a percentage of the total number of beds available on the PICUs.

On November 9, 2009, the CIb/GR committee also advised maintaining a two-dose vaccine schedule because there was still insufficient evidence that a single dose of vaccine would be able to provide people with a broad and long-term pandemic virus protection. According to the previous CIb/GR supplementary advice document, dated September 17, 2009, there should be a minimum interval of 3 weeks between the two H1N1 pandemic vaccinations [I, September 17, 2009]. In addition, there should also be a minimum of 2 weeks between the yearly seasonal flu vaccination and the 2009 H1N1 pandemic vaccination. Finally, the advice relating to vaccinating pregnant women from the second trimester was tightened up. Based on recent information, it was clear that pregnancy – even in women without underlying conditions – was itself a risk factor for complications developing from an infection with the 2009 H1N1 pandemic virus. For this reason, the vaccine for this group of patients was not only made available but also recommended by the CIb/GR committee [I, November 9, 2009]. Again, this supplementary advice was uploaded to the CIb flu website.

On November 9, 2009, the Minister of VWS accepted the recommendations made by the CIb/GR Council committee. This meant that the regional GGDs had to vaccinate children aged 6 months to 4 years, as well as their household members, in the first round of a mass vaccination campaign starting on November 23, 2009 and lasting until November 28, 2009. The influenza coordinators were duly and confidentially informed of this step on November 6, 2009 by VWS and GGD NL [C, November 10, 2009].

On November 10, 2009, the instructions for preparing Focetria® were amended by the LCI and distributed once more via Inf@ct. Based on information supplied by Novartis, the preparation instructions for Focetria® stated that once the multi-dose container had been opened, the remaining doses should be used within 28 days. However, on November 6, 2009, the EMEA determined that this period should be brought in line with that set for the shelf life of the Pandemrix vaccine – which was a period of 24 hours as long as the vaccine, once opened, had been kept at a temperature of between +2 °C - +8 °C [B, November 6, 2009].

In spite of this, the instructions for preparing Focetria® were not amended [C, November 10, 2009]. These changes led to a lot of confusion in the field and were the cause of many questions directed by GPs to the call centre, the LHV and the NHG.

The vaccine administered in the mass vaccination campaign conducted by the regional GGDs (6 months to 4 years and household members of babies up to 6 months) was Pandemrix®, produced by GlaxoSmithKline. The product characteristics of Pandemrix® (that was supplied with the fixed needle syringe) and the Dutch language patient leaflet was uploaded to the CIb flu website in early November 2009. On this website, PowerPoint presentations with background information on vaccinations for the 2009 H1N1 pandemic virus and general information on influenza were also made available [C, November 10, 2009].

Focetria® (Novartis) is an inactivated, adjuvanted human vaccine for influenza that is grown from chicken eggs
Focetria® was used by GPs to vaccinate people in the regular risk groups; its use was extended to include pregnant women in the second or third trimester. People working in the health care sector were vaccinated with this vaccine by their company doctor or occupational health and safety service.

Pandemrix® (GlaxoSmithKline) is also an inactivated, adjuvanted human vaccine for influenza that is grown from chicken eggs. Pandemrix® is used by regional GGDs to vaccinate children up to the age of 5 years and household members of babies under the age of 6 months. Pandemrix® is supplied in separate vials – one contains the antigen and one contains the adjuvant – and has to be mixed by staff at the regional GGDs.

For the above two vaccines, it goes without saying that in one person, both of the two doses required must be the same vaccine type.

The RCP was very closely involved in the activities surrounding the GGD mass vaccination campaign for children aged 6 months to 4 years and the household members of babies up to the age of 6 months. As well as the involvement of the RCP with all the regional GGDs involved in the campaign, about half of the GGDs had organized their vaccination rounds jointly with another GGD or some other organization such as the GHOR, the local authority, a home care organization, baby and toddler clinic or regional public safety service. Within the structure of the regional GGDs, it was the general health departments who took control of organizing the campaign in about half of the total regions. In other regions, the department taking charge was that of the youth health care service (JGZ), the GHOR or in some cases collaborative efforts of several departments [32].

Five RCP regional offices distributed 1.21 million doses of vaccine to a centralized GGD or other vaccination location during the 2009 H1N1 pandemic vaccination campaign; the vaccine was supplied by the NVI. In addition, the RCP had other tasks that included collating the data

(names and addresses), calling people up for vaccinations (written invitations with registration cards were sent in week 47 of 2009), registering the vaccines that had been administered in InfluSys and finally reporting the attendance rate for this part of the vaccination campaign [35].

InfluSys is a national database designed by the RCP for the national registration of 2009 H1N1 pandemic vaccinations. This database is a clone of Praeventis, the information system used by RCP for the registration of vaccinations for the national vaccination programme. With the help of InfluSys, the registration cards and vaccination stamps can be printed and sent and the administered vaccinations can be registered [35].

In the Inf@ct message sent on November 10, 2009, the LCI reported that in the English language patient leaflet that had been distributed with the Focetria® vaccines in the Netherlands, it was incorrectly stated that any allergy to antibiotics constituted a contraindication for the vaccine. However, the Dutch language patient leaflet contained the correct information: only an allergy to kanamycine or neomycine was a contraindication for the vaccine. The correct information was conveyed to GPs in the Netherlands via the SNPG. In consultation with the NHG, the recommendations for vaccination of people with blood clotting abnormalities were clarified. The guideline drawn up for this purpose was made available to GPs via the NHG website [C, November 10, 2009].

On November 10, 2009, the RCP reported (via RVP News) that the 2009 H1N1 pandemic vaccination had consequences for the RVP. In between the vaccination for 2009 H1N1 pandemic flu and the RVP vaccinations, it was preferable to have an interval of two weeks. This meant that due to the large-scale vaccination campaign for 2009 H1N1 pandemic flu, from November 10, 2009 onwards, some RVP vaccinations had to be deferred. Specifically, this meant that for children born after November 23, 2004 and before May 23, 2009, the following vaccinations were postponed:

- diphtheria, tetanus, whooping cough, polio, HIB disease, hepatitis B and pneumococcal vaccine cocktail at the age of 11 months;
- MMR and MenC at the age of 14 months;
- diphtheria, tetanus, whooping cough, polio at the age of 4 years.

The postponed RVP vaccinations should still be given after those for the 2009 H1N1 pandemic virus. The vaccination of infants at birth (hepatitis B) and 2, 3, and 4 months should be continued normally. In spite of the RVP vaccinations being postponed, the risk of children developing one of the diseases covered was still small. This was because of the vaccinations that children received at the ages of 2, 3, and 4 months, the low incidence of disease through long running vaccination programmes, and to the fact that group immunity has been built up. According to the RCP newsletter, the risk of developing 2009 H1N1 pandemic influenza was greater [36].

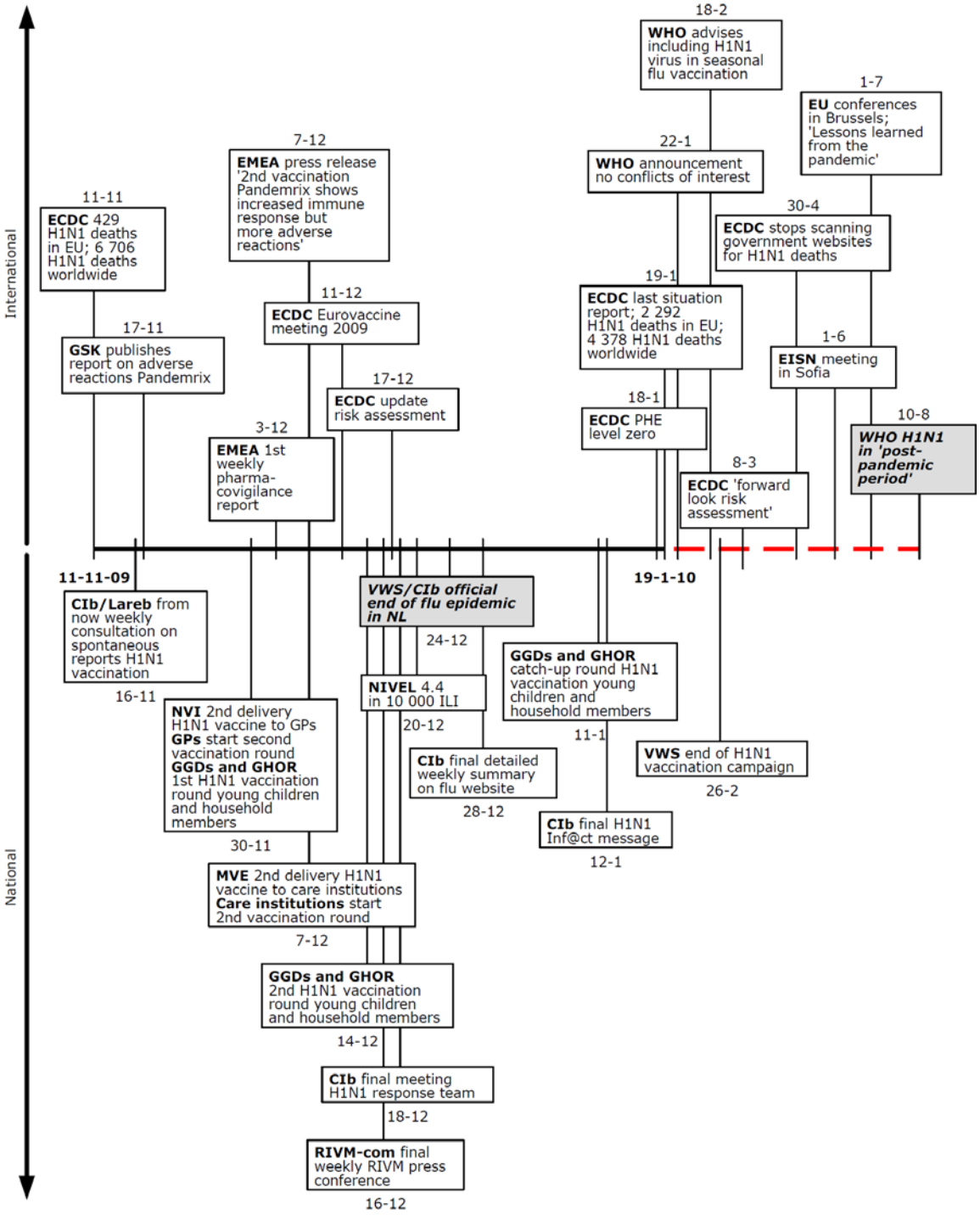

Figure 7 Chronological overview of national and international activities and events with regard to the 2009 H1N1 pandemic for the period November 11, 2009 to August 10, 2010.

8 Period 6: November 11, 2009 to August 10, 2010

Decrease in the number of 2009 H1N1 influenza cases in the Netherlands and the WHO declaration of the end of the pandemic
Period 6 represents the final phase of the pandemic in the Netherlands. This phase started with the peak of the 2009 H1N1 influenza epidemic in the Netherlands and was further characterized by a subsequent decrease in the number of pandemic influenza cases. The epidemic of 2009 H1N1 influenza ended in the Netherlands in December 2009. The vaccination campaign for the 2009 H1N1 virus ended in the Netherlands on February 26, 2010. The WHO declared that the pandemic was officially over on August 10, 2010.

8.1 Situation

8.1.1 International

On November 12, 2009, the ECDC reported 429 deaths resulting from an infection with the 2009 H1N1 virus in Europe and 6277 deaths in the rest of the world [B, November 12, 2009]. There was a wide disparity in Europe with some countries reporting an increase in 2009 H1N1 influenza activity whilst others reported a decrease [E, November 13, 2009].

On November 27, 2009, all 27 EU countries and the 4 EFTA countries reported cases of 2009 H1N1 pandemic influenza to the ECDC. At that point in time, the ECDC had received 825 reports of deaths resulting from infection with the new virus since April 2009. In Europe, the number of deaths increased steadily from week 41 onwards. At that time, most of the victims in Western Europe had been reported but the number of deaths resulting from the 2009 H1N1 pandemic virus was still slowly increasing in Central and Eastern Europe [B, November 27, 2009].

On December 1, 2009, it was evident from reports published by the CDC and the health authorities in Canada, that influenza activity in the US and Canada was continuing to abate. By contrast, the ECDC reported an increase in the number of 2009 H1N1 pandemic cases in Europe [B, December 1, 2009].

By early December 2009, a decreasing trend in 2009 H1N1 influenza activity could be observed worldwide, and this was especially evident in Western Europe, the US, and in Canada. However, precisely the opposite was happening in Eastern Europe, where an increasing trend of influenza activity could be seen [E, December 11, 2009].

On December 14, 2009, it became clear from reports from the EISN that influenza activity was widespread in most European countries. However, 13 European countries had been reporting a decrease in the number of people with an influenza-like illness for the previous 2 weeks. Up to this point in time, 1333 deaths caused by the 2009 H1N1 pandemic virus had been reported in Europe. Outside Europe, the ECDC had reported 9530 deaths resulting from the pandemic virus [B, December 14, 2009]. The estimates of the total number of deaths in the US from the pandemic virus, made by the CDC on December 15, 2009, were much higher. According to the CDC, there had been nearly 10,000 deaths resulting from the pandemic in the US alone. The CDC once more reported that influenza activity in the US was decreasing [B December 15, 2009].

On December 21, 2009, it was evident from data collated through the EISN that most EU countries had reported an average intensity of influenza activity. Only 5 countries

had reported high levels of influenza activity. Furthermore, 19 countries had been reporting a decrease in the number of cases of influenza-like illness or an acute respiratory infection for the past two weeks [B, December 21, 2009].

On December 31, 2009, it was evident from the CDC flu maps that compared the seasonal influenza (influenza type A (H3N2)) with the 2009 H1N1 pandemic virus, that the H1N1 virus was the dominant influenza strain in all Northern continents. At this time, the ECDC reported that there had been 1923 deaths in Europe and 11,047 deaths outside Europe that had resulted from infection with the 2009 H1N1 pandemic virus [B, December 31, 2009].

According to the ECDC's weekly surveillance overview – which was based on data from the EISN – published on January 11, 2010, all EU countries had reported low to average influenza intensity in their populations. This led to a decrease or stabilization of the level of influenza activity in most countries. Moreover, the number of SARI cases also continued to decrease [B, January 11, 2010].

On January 19, 2010, in the final ECDC daily pandemic update, it was reported that there had been a total of 2292 deaths resulting from pandemic flu infection in Europe; outside Europe the number of flu-related deaths was 12,086 [B, January 19, 2010].

Up until August 1, 2010, approximately 18,449 patients had died worldwide due to the effects of the 2009 H1N1 pandemic virus. The WHO reported that on a worldwide level, more than 214 countries and overseas territories had reported cases of 2009 H1N1 flu during the pandemic.

On August 10, 2010, the DG of the WHO announced that the 2009 H1N1 influenza pandemic had officially come to an end. After this date, the world was in a post-pandemic period.

8.1.2 National

By November 13, 2009, there had been a total of 909 cases of 2009 H1N1 pandemic flu infection admitted to hospital in the Netherlands; each day about 40 new hospital admissions were added to this total. Of these hospital admissions, 20% were children up to the age of 5 years. During the week of November 13, 2009, in the Netherlands, 19 people were admitted to an ICU and 5 patients died as a result of their H1N1 flu infection. The incidence of 2009 H1N1 pandemic flu in the Netherlands was 15 per 10,000 inhabitants [E, November 13, 2009].

In mid November 2009, the ECDC made a recalculation of the expected number of people ill, hospital admissions and deaths relating to infection with the 2009 H1N1 pandemic virus. The ECDC based this on the information available at the time from various countries with regard to the progression of the pandemic. Based on this recalculation, the EPI adjusted the assumptions that had been made for the Netherlands and documented this in the memorandum which translates as 'Updated assumptions for pandemic planning'. The CIb said that it should be noted that this document was concerned with predictions and that the actual data may ultimately differ. If the regional GGDs wanted to determine the burden of disease in their own region, the CIb advised using the updated assumptions from the CIb because the use of other scenarios could lead to confusion [B, November 12, 2009; C, November 19, 2009].

Around November 20, 2009, the number of flu-related hospital admissions in the Netherlands rose to an average of 50 admissions per day. During this week, 359 cases of 2009 H1N1 pandemic flu were admitted to hospital, 38 of which were on an intensive care unit. Moreover, 6 more deaths were reported – all these patients had had severe underlying conditions. This brought the number of deaths in the Netherlands up to this point to 28. On November 20, 2009, the CIb also reported the second case of a patient with an infection of 2009 H1N1 flu that was resistant to oseltamivir [E, November, 2009].

On November 27, 2009, the CIb reported that the number of admissions to hospital in the Netherlands, including those on ICUs was decreasing. The surveillance data from the CMR monitoring stations showed that the number of consultations for an influenza-like illness per 10,000 inhabitants was also decreasing [E, November 27, 2009].

By December 9, 2009, there were eight patients in the Netherlands diagnosed with an infection of 2009 H1N1 pandemic virus that was resistant to the antiviral agent oseltamivir – with which they had been treated. In all eight cases, there were no indications that the viruses were naturally resistant to the drug although it was assumed that the resistance had developed as a result of prolonged long-term treatment with oseltamivir. The patients had been excreting the influenza virus for some time and in six of the eight patients this was probably due to disturbances in the immune system. Three of the above patients died; they had underlying conditions for which they had been treated with chemotherapy. Up to that point, no laboratory-confirmed cases of transmission of the resistant influenza virus had been found in any contacts of the eight patients who had died [C, December 9, 2009].

On December 11, 2009, the CIb announced that the number of hospital admissions in the Netherlands had once again decreased. On December 18, 2009, the CIb reported that the incidence of the 2009 H1N1 pandemic virus was decreasing/had decreased sharply. At that point in time, the GP consultation ratio for influenza-like illness was just above the baseline at 5.7 per 10,000 inhabitants. The CIb expected the influenza activity to fluctuate around the baseline for a few weeks. The CIb continued to follow the epidemiological developments of the 2009 H1N1 pandemic closely because the risk of a second wave of influenza in the following spring could not be disregarded [C, December 18, 2009].

On December 20, 2009, it was evident from the CMR monitoring stations surveillance data that, up to that point, 4.4 in 10,000 people in the Netherlands, had consulted their GP because of influenza-like illness – this was far under the baseline. On December 24, 2009, the CIb and the Ministry of VWS announced that the 2009 H1N1 influenza pandemic had officially ended in the Netherlands. With this announcement came the report that up to December 24, 2009, 2156 patients had been admitted to hospital in the Netherlands and 53 patients had died as a result of the 2009 H1N1 pandemic. The percentages of patients found to have underlying medical problems were 57% of those admitted to hospital and 90% of the patients who had died.

In mid January 2010, the CIb reported that a total of 2182 cases of 2009 H1N1 influenza infection had been admitted to hospital and 54 patients had died. Up until the week of June 7, 2010, 63 patients had died as a result of 2009 H1N1 pandemic virus infection. On July 8, 2010, the CIb reported that the number of hospital admissions and deaths from H1N1 influenza infection had remained stable for several weeks.

In weeks 24 through 35, 2010, the total number of hospital admissions in the Netherlands from 2009 H1N1 pandemic infections remained constant at 2192. In week 36 of 2010, there was 1 new hospital admission resulting from H1N1 flu infection which brought the total up to 2193 hospital admissions.

8.2 Diagnostics

8.2.1 International

On November 18, 2009, the WHO published an article summarizing the characteristics of 39 cases of 2009 H1N1 virus infection (from worldwide reports) that were resistant to oseltamivir. Nearly all these cases appeared to have developed resistance to oseltamivir after treatment or prophylaxis with this antiviral agent. Of the 39 cases of resistance, 7 had immune suppression. The authors concluded that resistance to oseltamivir during the 2009 H1N1 pandemic was a very rare occurrence. On the same point, however, there had been no cases reported of resistance to zanamivir [B, November 18, 2009].

8.2.2 National

On December 17, 2009, in a Labinf@ct message, clinical microbiologists were advised by the LIS to keep diagnostic tests for the 2009 H1N1 pandemic virus in the diagnostic package for respiratory diseases. This advice was given because the H1N1 virus could have serious consequences for patients at high risk. Rapid diagnostic tests were still necessary so that treatment with antiviral agents could be started on time for patients at high risk of complications [D, December 17, 2009].

8.3 Control

8.3.1 International

On December 18, 2009, the WHO advised conducting more serological testing. Serological testing enables essential information to be gathered which leads to the development of more robust models and more data relating to the progression of the pandemic. For example, serological tests can show which part of the population is susceptible to the virus. Furthermore, according to the WHO, serological testing can help provide a good foundation for policy measures taken during a pandemic [B, December 18, 2009].

On April 30, 2010, the ECDC stopped scanning the websites of national governments to collate data on victims of the 2009 H1N1 virus as reports of these patients made by the relevant governments were no longer collected by the ECDC.

8.3.2 National

Within the framework of pandemic control, it was important to monitor the effectiveness of the 2009 H1N1 influenza vaccination campaign. The questions in Osiris about vaccination and underlying conditions were an important source of information to this end. Therefore, on December 9, 2009, the regional GGDs were requested by the EPI and the LCI to answer the questions in Osiris as completely as possible. The questions in Osiris were slightly amended on December 10, 2009 so that the information could be collated more easily by the CIb. One regular occurrence was that the doctor treating a patient in the hospital did not have any information on the vaccination status of a patient. To this end, the LCI asked the regional GGDs to obtain vaccination information via a patient's GP in the case of patients who were eligible for influenza vaccination by their GP, for example, people with underlying medical conditions and people over the age of 60 years. Sometimes this information had to be obtained directly from the patient because not all GPs had registered the vaccinations they had administered. In cases of illness in otherwise healthy children

under the age of 5 years, the CIb later tracked down the vaccination data via the RCP [C, December 9, 2009].

Due to the importance to public health (early detection, spread, resistant strains) and in order to gain a good picture of the background and progression of the illness in patients with a resistant virus, the procedure for reporting resistance was distributed by the LIS and the LCI on December 9, 2009, via an Inf@ct message. This procedure was as follows:

- The laboratory found the virus with a resistant mutation.
- The laboratory alerted the RIVM and the local GGD.
- The LIS virologist filled out the notification form together with the laboratory as far as possible and then alerted the LCI (a sample letter on this subject was sent through an Inf@ct attachment to all those involved).
- The LCI registered the person (case) and contacted the relevant local GGD.
- The notification form was further filled out by the laboratory and the LCI and returned to the virologist at the LIS.
- The LCI and the regional GGDs agreed on contact investigation in clinical settings and for family contacts and ensured that any samples were analyzed at the RIVM. Contact investigation for family contacts was focussed mainly on contacts who now had or had previously had symptoms fitting the pattern of influenza in the period that the index patient had been excreting the resistant virus. Contact investigation in the clinical setting was discussed by the GGD with the hospital hygienist or other professional responsible for the prevention of infection. The results were passed on to the LIS virologist to be entered on the notification form.
- The RIVM was keen to receive samples from patients with resistant influenza strains for the further investigation of virulence markers.

This procedure was also distributed to the OALs and through Labinf@ct. At international level, the notifications were sent to the ECDC and the WHO [C, December 9, 2009].

In mid December 2009, the GGD-Osiris questionnaire was amended with regard to the following points:

- extra questions were added relating to a person's vaccination status;
- the date of notification by the GGD was added;
- some questions with regard to antiviral agents were removed.

As part of the surveillance and the monitoring of resistance, the CIb considered it important to keep a close eye on the progression of the pandemic in the Netherlands. To this end, the LCI requested the regional GGDs (via an Inf@ct message) to maintain their former work activities relating to the 2009 H1N1 pandemic. The CIb expected that the number of hospital admissions would continue to fall in the following weeks; this would reduce the work pressure for the regional GGDs. The compulsory notification that had been in place since August 15, 2009 – for patients who had died or been admitted to hospital as a result of the 2009 H1N1 pandemic virus – remained unchanged [C, December 18, 2009]. This information was repeated in the Inf@ct message of January 12, 2010 because a second wave of flu in the future could not be ruled out [C, January 12, 2010].

In the final Inf@ct message on the 2009 H1N1 pandemic, circulated on January 12, 2010, the regional GGDs were informed about the scaling down operation by the LCI. Throughout the pandemic, general practices, regional GGDs and hospitals had undergone a scaling up operation that had been based on local crisis plans. Because the wave of pandemic influenza appeared to be over, the scaling down operation

could now be started in accordance with plans agreed at local level. Contained in the same Inf@ct message was the following recommendation from the WIP: 'If patients present with a respiratory infection at a hospital, then it is no longer necessary to nurse these patients in droplet and/or contact isolation while waiting for the result of the diagnostic test for the 2009 H1N1 pandemic virus'. This was a deviation from the policy in favour of isolation that had previously been upheld; the change was made because the incidence of H1N1 flu in the population had become so low that there was no longer an on-going influenza pandemic. This meant that the mathematical probability of the 2009 H1N1 virus being present in someone with a respiratory infection was low. The WIP said, however, that policy could differ for individual patients, for example, a patient who presented with pneumonia that had developed following contact with someone who was infected with the 2009 H1N1 pandemic virus. In hospitals where the influenza virus was known to be circulating, patients were nursed in droplet isolation. With regard to patients who presented with respiratory symptoms at an emergency department, the hospital had to comply with the standard precautionary measures. The policy for general practices could be found on the NHG website [C, January 12, 2010].

In the final Inf@ct message (as above) of January 12, 2010, the LCI reported that the Ministry of VWS had purchased a small supply of 100 courses of the non-registered antiviral agent zanamivir IV. Zanamivir is registered as an inhalation drug, but is difficult to administer to patients through this route. Zanamivir IV is normally administered through the bloodstream. Whilst the 2009 H1N1 pandemic seemed to be abating in the Netherlands, zanamivir IV was still offered to patients because it added to the treatment options for patients who were seriously ill or those who had developed resistance to oseltamivir. The NVI managed this supply of antivirals. The hospital pharmacies at the academic medical centres each received three courses of zanamivir IV and could supply the general hospitals in the Netherlands as required. Because these courses of zanamivir were not registered, the drug could only be administered under doctor's orders. This information was circulated to all hospital pharmacies. Up to this point, zanamivir IV had only been available in the 'compassionate use' programme run by GSK. Consequently, only limited experience had been gained with zanamivir IV in the Netherlands. The Dutch Health Care Inspectorate and the Medicines Evaluation Board had given approval for zanamivir IV to be used up to December 15, 2009. The guidelines for treatment with zanamivir IV could be found on the CIb flu website [C, January 12, 2010].

8.4 Government communications

8.4.1 International

On November 11, 2009, the ECDC published the document 'Pandemic (H1N1) 2009 planning assumptions to end of May 2010 for EU/EEA countries'. Many organizations – including the EPI – worked on producing this international document.

Around November 16, 2009, in the light of the 2009 H1N1 pandemic, the WHO published a document which took into account the preparations required for large public events [B, November 16, 2009].

On December 3, 2009, the first weekly report on authorized pandemic vaccines and antiviral agents was published ('pharmacovigilance report') by the EMEA. This report described the use, the advantages and the reported adverse reactions of these substances [B, December 4, 2009].

On December 17, 2009, the ECDC's risk assessment for the 2009 H1N1 influenza pandemic was amended for the seventh time and published on the ECDC website [B, December 17, 2009].

On December 22, 2009, the WHO published a press release in which the accuracy of the assessment of the epidemiology of the pandemic was discussed. The WHO was still assessing the 2009 H1N1 pandemic as a mild pandemic; people in younger age groups had been more affected by this new virus than during an outbreak of 'normal' seasonal influenza [B, December 23, 2009].

On December 28, 2009, the WHO held a press conference. During this meeting, the DG of the WHO said that it was still too early to be able to conclude that the pandemic was actually over. According to the WHO, influenza activity was still high in some parts of Europe and Asia. The DG of the WHO expected to still see several peaks of influenza activity in various parts of the world [B, December 31, 2009].

On January 19, 2010, the last daily update on the 2009 H1N1 pandemic was circulated by the ECDC [B, January 19, 2010].

On March 8, 2010, the ECDC published the document: 'Forward look risk assessment for the 2009 pandemic influenza A (H1N1) and future influenza season' [37].

On July 21, 2010, the WHO issued an explanation for the possible conflicts of interest that had occurred. The WHO reported that no commercial interests had played any role in the decision-making procedures for the 2009 H1N1 pandemic. The WHO also said that it recognized the potential risk of conflicts of interest occurring in the relationship between an organization such as the WHO and a commercial enterprise. For this reason, the WHO indicated in its message that it would be evaluating its own response and reaction to the H1N1 pandemic.

8.4.2 National

On November 16, 2009, the memorandum translated as: 'Updated assumptions for pandemic planning' was issued by the EPI. This memorandum (and others) were placed on the CIb flu website.

On December 16, 2009, RIVM-com organized the last weekly CIb press conference.

On December 17, 2009, the final message about the 2009 H1N1 pandemic was sent through Labinf@ct. On January 12, 2010, the final message on the flu pandemic was sent through Inf@ct.

On December 24, 2009, the CIb (via RIVM-com) and the Ministry of VWS officially announced that the epidemic of 2009 H1N1 influenza was over in the Netherlands.

On December 30, 2009, the last Influenza Surveillance Newsletter on the 2009 H1N1 pandemic virus was issued by the NIC, *Nieuwsbrief Influenza surveillance 2008/2009* volume 18, number 17. This newsletter stated that the influenza epidemic in the Netherlands was over.

In the period from April 28, 2009 up to December 30, 2009, **22 influenza surveillance 2008/2009 newsletters were issued by the NIC.**

From January 1, 2010, the CIb weekly summaries were no longer placed on the CIb flu website. In addition, no more PowerPoint presentations were made from the

information contained in those weekly summaries. The surveillance was, however continued by the EPI and the findings were included in the reports from the expert meetings for disease detection. The number of hospital admissions and deaths were – from that time on – still being published on the CIb flu website by the EPI.

Data upload to TESSy (WHO, ECDC)

From January 18, 2010, the EPI no longer needed to make double reports to EuroFlu (WHO) and TESSy (ECDC). From this date onwards, reporting to TESSy alone was sufficient because data was forwarded automatically to EuroFlu. The following data were reported to TESSy from January 18, 2010:

- Reporting of routine virological influenza and RSV results..
- Aggregated data: cumulative number of laboratory-confirmed cases of hospital admission and deaths caused by the 2009 H1N1 pandemic virus and subdivided according to age group.
- Individual data: individual data on the SARI cases in respect of demographics (age, sex), date of onset of symptoms, date of hospital admission, notification date, treatment, prophylaxis, underlying complaints, ICU admission, and yes/no mortality.

In 2010, during international meetings of experts and by request, CIb professionals gave various presentations on the 2009 H1N1 pandemic. For example, during the ECDC Advisory Forum on February 17, 2010, a presentation was given by someone from the EPI: 'Pandemic vaccination in the Netherlands'. On March 22, 2010, during a meeting in Brussels – which was organized by the Belgian authorities – the EPI gave a presentation on the Netherlands vaccination campaign: 'Vaccination against influenza A/H1N1v in the Netherlands'. Another presentation given by the EPI was 'Lessons from the 2009 Pandemic Influenza', this was given in Boston on June 15, 2010, during the Symposium Surveillance for Decision Making in Emerging Diseases.

Statistics for RIVM-com surrounding the 2009 (H1N1) pandemic (April 2009 to January 2010)

- 54 messages sent through Inf@ct;
- 14 messages sent through Labinf@ct;
- 22 RIVM press conferences (including 3 update sessions) organized by RIVM-com;
- 28 CIb weekly summaries placed on the CIb flu website by EPI;
- 17 PowerPoint presentations by the EPI from the information in the CIb weekly summaries;
- 48 newsletters compiled by RIVM-com and placed on the RIVM homepage;
- more than 200 media announcements (radio and TV) made by RIVM-com;
- approximately 1.5 million people visited the CIb flu website in the period April 28 to December 31, 2009. At the peak of the pandemic, the site had 10,000 visitors per day.

Figures for incoming telephone calls to the 7000 number at the LCI (2008 and 2009)

Month	2008	2009
January	477	572
February	491	493
March	524	570
April	521	661
May	486	1020
June	548	1618
July	669	1354
August	446	872
September	524	748
October	580	796
November	566	1045
December	415	723

Incoming telephone calls to the department for safety monitoring of the National Vaccination Program (RVP): The telephone service at RVP (the 2424 number and the 1801 alternative) received 35% more telephone calls in September and October 2009 compared with the same months in the previous year. In November 2009, this increase rose to as much as 600% compared with the previous year (676 in 2008 and 4051 in 2009). In December 2009, the increase was comparable to the previous year.

8.5 Meetings

8.5.1 International

On December 3, 2009, the WHO held a press conference in which they announced that it was still too early at that time to conclude that the peak of the 2009 H1N1 pandemic had passed [B, December, 2009].

On December 11, 2009, the first meeting of Eurovaccine 2009 was held in Stockholm. This was the first European conference on vaccination and immunization that had been organized entirely by the ECDC. The aim of this meeting was to create a platform where professionals could exchange information on the pandemic virus [37].

The annual conference meeting of EISN was held in Sofia, Bulgaria from June 1 to June 4, 2010. Professionals from the EPI and the LIS attended this meeting.

On July 1 and 2, 2010, a conference: 'Lessons learned from the influenza pandemic A (H1N1) 2009' was held in Brussels; this had been organized by the European Commission, under the auspices of the Belgian Presidency of the EU. This conference was focussed on the evaluation of the influenza pandemic within the EU and WHO context. Some of the content for this conference had come from the recent EISN meeting in Sofia. The Brussels meeting was attended by professionals from the EPI, the LIS and the Ministry of VWS.

On July 5, 2010 an informal meeting of the Health Council of the Netherlands was held under the auspices of the Belgian Presidency of the EU. During this meeting, the outcomes of the 'Lessons learned….' conference of July 1 and 2, 2009 were discussed.

On August 10, 2010, the WHO Emergency Committee held its ninth meeting through the medium of a teleconference. After this meeting, the DG of the WHO announced that the 2009 H1N1 pandemic was officially over. From that time, the world entered the post-pandemic period.

8.5.2 National

On December 16, 2009, the last meeting of the VWS policy team for crisis containment (BTCB) was held at the Ministry of Health, Welfare and Sport. The last meeting of the response team at the CIb was held on December 18, 2009, [E, December 18, 2009].

The CIb response team met 77 times to discuss issues relating to the 2009 H1N1 pandemic in the period from April 2009 to December 2009. In the same period, 4 OMT meetings were organized by the CIb.

8.6 Vaccination policy for the 2009 H1N1 virus

8.6.1 International

On November 11, 2009, the WHO started its weekly pharmacovigilance teleconferences in which countries worldwide could participate.

On November 17, 2009, GSK published a report describing the adverse reactions of Pandemrix. Only a few cases of adverse reactions had been reported – two cases of anaphylactic shock in adults and otherwise mainly local side effects [E, November 17, 2009].

On November 23, 2009, the EMEA concluded from the latest available information on the vaccines Focetria (Novartis) and Pandemrix (GlaxoSmithKline) that just 1 dose would be enough to create an immune response that would be sufficient to provide protection from the 2009 H1N1 virus to people between the ages of 10 and 60 years. Moreover, according to the EMEA, Pandemrix could also be used as a single dose for older people. For some patient groups, however, such as young children and immunocompromised patients, the EMEA recommended 2 doses [B, November 23, 2009].

In the message sent on November 23, 2009, the EMEA announced that any adverse reactions that occurred as a result of the 2009 H1N1 pandemic vaccine would continue to be monitored by the EMEA and by other national institutions. At that point, there had been only relatively mild adverse reactions reported for the three authorized vaccines; these were fever, nausea, headache, allergic responses and skin reactions around the vaccination site. According to the EMEA, there had been a very small number of cases of serious adverse reactions, such as Guillain-Barré syndrome and foetal death reported by patients who had been vaccinated with a pandemic flu vaccine. Based on the collated data, the EMEA concluded that there was no connection between these severe adverse effects and the vaccines [B, November 23, 2009].

On December 3, 2009, the EMEA published its first weekly pharmacovigilance report.

On December 7, 2009, the EMEA brought out its advice regarding the possibility of fever in young children following vaccination with the pandemic vaccine. The EMEA said that young children were at increased risk of developing mild fever after they had been given the second vaccination of Pandemrix. Reports of fever developing in children in the Netherlands after the first vaccination with Pandemrix had also been received at Lareb. Prior to this, fever had not been indicated as a possible adverse reaction and GPs were receiving numerous questions on this issue. The EMEA advised checking the body temperature of children who had been vaccinated and, if necessary, taking measures to bring down the temperature – for example, by giving paracetamol. The EMEA emphasized that new clinical research in children between the ages of 6 months and 3 years had shown that the immune response was clearly higher following the second dose of Pandemrix [C, December 7, 2009].

Around December 31, 2009, the EMEA published its fourth weekly pharmacovigilance report. In this report, the EMEA stated that at least 218,000 pregnant women in Europe had been vaccinated with 1 of the 3 authorized vaccines [B, December 31, 2009].

On January 7, 2010, the recommendations from the European Council (made during the meeting of December 22, 2009) on the seasonal flu vaccination were published in the Official Journal of the EU [B, January 7, 2010].

On February 18, 2010, the WHO recommended including the 2009 H1N1 virus in the yearly round of seasonal flu vaccinations for the autumn of 2010.

8.6.2 National

From November 16, 2009, weekly consultation took place between Lareb and the CIb with regard to the spontaneous reports concerning the 2009 H1N1 pandemic vaccination. The weekly spontaneous reports concerning the 2009 H1N1 pandemic vaccination were placed on the Lareb website from November 25, 2009 onwards.

In week 47 (November 16 to November 22, 2009) the NVI received a pre-alert from the vaccine manufacturer about the second delivery of the pandemic vaccines to the NVI. The second delivery of pandemic vaccines to the NVI took place in week 49 (November 30 to December 6, 2009).

The most significant medical points relating to the 2009 H1N1 pandemic vaccination were set out in a document during a meeting held on November 17, 2009, for those bearing final medical responsibility for the vaccination campaign for children and their household members. This document contained advice on how to prepare for a possible case of collapse and anaphylactic shock; clinical experts and the Dutch Health Care Inspectorate had been consulted for this purpose. Also added to the document was a note that the EpiPen junior could also be used for children from the age of 6 months. This document was distributed to relevant parties as an attachment to an Inf@ct message on November 19, 2009. The regional GGDs were asked to pass this information on to the person who held final medical responsibility for the H1N1 vaccination campaign (for children and household members) in their region [C, November 19, 2009].

The Inf@ct message of November 19, 2009, also contained – as attachments – a registration form and a report form for acute incidents following 2009 H1N1 pandemic vaccination were included. These 2 forms had been compiled by the LCI and had to be returned there after they had been completed [C, November 19, 2009].

During week 48 (November 23 to November 29, 2009), the first H1N1 vaccination round was carried out by the regional GGDs and the GHOR for children of 6 months up to and including 4 years and household members of babies up to the age of 6 months.

During weeks 47 and 48 (November 16 to November 29, 2009, GPs could place subsequent orders with the NVI for the second H1N1 vaccination round through the SNPG website. These were delivered to GPs by the NVI during weeks 49 and 50 (November 30 to December 13, 2009). During weeks 48 and 49 (November 23 to December 6, 2009) care institutions could place follow-up orders through the NVI website for the second H1N1 vaccination round; these vaccines were then delivered by the NVI in weeks 50 and 51. General practitioners and care institutions could then plan the second H1N1 jab at their own discretion. How this was done depended on a number of factors: there had to be a minimum of one to two weeks between the standard influenza vaccination and the vaccination against 2009 H1N1 influenza and a minimum interval of three weeks between the first and second H1N1 jabs.

On November 27, 2009, the Ministry of VWS announced that the cabinet had decided to sell the surplus supply of H1N1 flu vaccines to other countries that had a serious shortage of vaccines. The number of vaccines concerned was approximately 2 million – they had been ordered for the vaccination campaign being run by GPs, regional GGDs and care institutions. Minister Klink assumed, bearing in mind the course that the 2009 H1N1 pandemic had run, that there would be no need to offer the vaccine to people in the Netherlands other than those in the groups specified by the CIb and the GR. It was against this background that the Dutch cabinet decided to help other countries that, up to that point in time, had not been able to offer vaccination to their risk group populations. A limited supply of vaccines – approximately 2.2 million – would be retained to safeguard against any unexpected developments in the Netherlands. During the first few months of 2010, more than 17 million vaccines would be available for sale besides the original 2 million that had been sold in December 2009.

The second vaccination round run by the regional GGDs for children aged 6 months to 4 years and household members of babies up to the age of 6 months, was carried out in the period from December 14 to December 19, 2009. An extra vaccination round was held for these groups from January 11 to January 16, 2010 [35].

The vaccination campaign carried out by GPs was rounded off at the end of December 2009. GPs were advised by the LHV and the NHG to store any surplus of vaccines in sealed containers in the fridge until further notice. These vaccines could be used in the following weeks for anyone who regretted their original decision not to be vaccinated – but only those in medical risk groups – and, for example, for pregnant women who had then entered their third trimester. Together with the SNPG and the NVI, the CvB arranged for a reimbursement module to be added to the web application for orders which would enable GPs to claim reimbursement for the number of vaccinations they had administered. GPs could submit their claims from December 14, 2009 to February 1, 2010.

Vaccinees	Type of vaccine	Vaccine administrator	First vaccination round	Second vaccination round	Extra vaccination round
Medical risk groups	Focetria	GPs – with support from SNPG, CvB, NHG, LHV and NVI	From November 2, 2009	Own planning*	Not applicable
Pregnant women in their second and third trimester	Focetria	GPs – with support from SNPG, CvB, NHG, LHV and NVI	From November 2, 2009	Own schedule*	Not applicable
Medical professional groups	Focetria	Care institutions, in collaboration with health and safety services (supported by the CvB and NVI)	From November 9, 2009	Own schedule*	Not applicable
Children between the ages of 6 months and 4 years	Pandemrix	GGD/GHOR with support from the RCP and NVI	November 23 to November 28, 2009	December 14 to December 19, 2009	January 11 to January 16, 2010
Household members of babies up to 6 months	Pandemrix	GGD/GHOR with support from the RCP and NVI	November 23 to November 28, 2009	December 14 to December 19, 2009	January 11 to January 16, 2010

* The second H1N1 influenza jab could be scheduled by general practitioners and care institutions themselves depending on when the seasonal influenza jab had been given. An interval of 1 to 2 weeks had to be left between the standard influenza vaccination and the 2009 H1N1 vaccination and a further interval of 3 weeks between the two H1N1 jabs.

It was no longer possible to order 2009 H1N1 pandemic vaccines from the NVI after January 2010. On February 22, 2010, the CvB and the SNPG announced an estimate of the level of vaccination in the population for the 2009 H1N1 pandemic vaccination campaign via general practitioners (based on the weekly reports). These estimates were based on the number of vaccinations declared.

- For people in the medical risk groups, 64% had completed the vaccinations (2 jabs) for 2009 H1N1 pandemic influenza. 71.8% of people in the medical risk groups had received a minimum of 1 dose of vaccine against the 2009 H1N1 pandemic virus. This led to an upward correction later on. Based on 82% of the declarations from general practices, the attendance rate for people from medical risk groups for the second vaccination for 2009 H1N1 pandemic flu was 93% of those people who had received the first vaccination. The attendance rate for the first vaccination was 76%; this was based on information from the questionnaire filled out voluntarily by 35% of the general practices via the web application. These percentages combined indicate that an estimated 70% of people classed in medical risk groups received full vaccination (2 jabs) against the H1N1 virus from general practitioners.
- In the medical risk groups indicated for the seasonal influenza vaccination, 63.5% did receive this vaccination as well as at least one of the 2009 H1N1 pandemic flu jabs.

- In the group of participating general practitioners, 74.1% were vaccinated against the seasonal influenza and 88.9% against the 2009 H1N1 pandemic virus. In the group of general practice assistants, 74.1% were vaccinated against the seasonal influenza and 73.6% against the 2009 H1N1 pandemic virus.
- In 23.5% of the general practices, all members of the staff were vaccinated against both the seasonal influenza and the 2009 H1N1 influenza; 7.4% of practice employees were not vaccinated for either the seasonal influenza or the H1N1 influenza.

The vaccination status of general practice staff did not significantly influence the level of vaccination in the patient population [38].

According to the RCP, 62% of children in the age group 6 months to 4 years and 52% of the household members of babies up to the age of 6 months had been given two vaccinations by the regional GGDs. With regard to health care sector staff eligible for vaccination, 43% had been vaccinated twice. One point of interest here is that 63% of the hospital staff called up had been given the first vaccination and the rate of attendance for the second vaccination in this group (54%) was higher than the average percentage in the overall group of care providers [38].

In the Netherlands, approximately 10 million people were immunized against the 2009 H1N1 pandemic virus. Both during and after the vaccination campaign, Lareb continued to gather and analyze reports of adverse reactions to the vaccine. The majority of the reports were for mild adverse reactions, such as pain, or redness around the injection site; fever occurred primarily in vaccinated children [39].

In 2009, the NVI played a central role in the ordering, delivering and receiving of the pandemic vaccines. During the 2009 H1N1 pandemic vaccination campaign, the NVI distributed – within a very short space of time – 8.03 million doses of vaccine to general practitioners, 1.36 million doses to care institutions and 1.21 million doses to 5 RCP regional offices. A total of 21,300 doses of vaccine were required for the vaccination of military personnel on active duty. Furthermore, 110,500 doses of vaccine were supplied to the Dutch Antilles and Aruba [38].

In a letter to the House of Representatives, dated March 5, 2010, the Minister of Health, Welfare and Sport stated that a total of 14.07 million doses of Focetria (Novartis) and 3.16 million doses of Pandemrix (GlaxoSmithKline) had been supplied to the Netherlands. It was stated in the contracts that a further 10.93 million doses of Focetria and 5.84 million doses of Pandemrix would be supplied in 2010 [38].

The Minister of VWS ended the vaccination campaign for 2009 H1N1 pandemic influenza on February 26, 2010. From that date onwards, no further vaccines were issued on behalf of the government. In line with the end of the vaccination campaign, the Minister of VWS ordered the NVI to collect the vaccines that were left over. This took place between March 15 and 26, 2010. The CvB and the SNPG were also closely involved with collecting the leftover vaccines from GPs and care institutions. The SNPG took care of the communication with the GPs and the CvB the communication with the care institutions. To help with this, the call centre was kept open longer (although downsized).

However, some of the vaccines were no longer suitable for use and were destroyed in accordance with the protocolled statutory requirements. A buffer of 2.2 million vaccines (1.8 million Focetria and 400,000 Pandemrix) were retained by the NVI because there was still a risk that the virus would mutate – which could lead to certain groups of people becoming more ill and thus needing the vaccine for

protection against the virus. This volume of vaccines would enable 5 to 6 age cohorts to be vaccinated twice [38].

At the request of the GR, on March 26, 2010, the memorandum translated as 'Background memorandum on whether or not children aged up to and including 4 years and pregnant women should be vaccinated against the 2009 H1N1 pandemic virus in 2010' was issued by the EPI.

In mid April, 2010, a study into the 2009 H1N1 virus vaccination level in pregnant women was started in the Netherlands.

In the letter from the Minister of VWS to the House of Representatives, dated May 12, 2010, it was clear that Novartis was not prepared to reduce the quantity stated in the vaccine order. This meant that the full quantity of the order was delivered. From this supply, more than 9.5 million doses of vaccine were distributed to users. According to the Minister of Health, Welfare and Sport, what was left over from this supply would be destroyed after the date of expiry, in accordance with legislative and regulatory requirements, unless no further parties came forward to purchase the vaccines. After agreement had been reached, GSK finally supplied 6 million doses of vaccine instead of the 9 million doses originally ordered. According to the contract, the adjuvant contained in the GSK vaccine still had a shelf life of 3 years following the date of delivery. A few countries took up the offer made by the Ministry of Health, Welfare and Sport to purchase 2009 H1N1 pandemic vaccines. These countries were Estonia (100,000 doses), Macedonia (80,000 doses), Surinam (50,000 doses) and Lithuania (27,000 doses) [40].

9 Research studies and publications from the CIb on the 2009 H1N1 influenza pandemic

9.1 Research from the CIb on the 2009 H1N1 influenza pandemic

Below is a list of the research (Dutch only) on the 2009 H1N1 pandemic set up by the CIb, including some ongoing studies.

Project no.	Description	Financer	Project manager	Start	Finish
V/205062/01	Nieuwe Influenza A vaccinatiecampagne	VWS	Maas, drs. N.A.T. van der	01-01-2010	31-12-2011
V/205094/01	Grieppandemie en de bedrijfsgezondheidszorg	SZW/A&O	Beaujean, drs.ing. D.M.J.A	01-01-2010	31-12-2010
V/210182/01	Serosurvey for the 2009 H1N1 virus	VWS	Sande, dr. M.A.B. van der	01-01-2010	31-12-2010
V/210702/01	Epidemiologische surveillance (H1N1)	VWS	Hoek, dhr. W. van der	01-01-2010	31-12-2010
V/230192/01	Diagnostiek en microbiologische surveillance	VWS	Meijer, dr. A.	01-01-2010	31-12-2010
V/230354/01	Swine-origin Influenza A H1N1	ZonMw	Koopmans, dr. M.P.G.	01-08-2009	01-12-2010

9.2 Publications from the CIb on the 2009 H1N1 influenza pandemic

Below is a list of the national and international publications from the CIb relating to the 2009 H1N1 pandemic. Updated till December 2010.

9.2.1 International

Asten L van, Lubben M van der, Wijngaard C van den, Pelt W van, Verheij R, Jacobi A, Overduin P, Meijer A, Luijt D, Claas E, Hermans M, Melchers W, Rossen J, Schuurman R, Wolffs P, Boucher C, Schirm J, Kroes L, Leenders S, Galama J, Peeters M, Loon A van, Stobberingh E, Schutten M, Koopmans M. Strengthening the diagnostic capacity to detect Bio Safety Level 3 organisms in unusual respiratory viral outbreaks. J Clin Virol. 2009 Jul;45(3):185-90. Epub 2009 Jun 6. Erratum in: J Clin Virol. 2010 Feb;47(2):204.

Boven M van, Donker T, Lubben M van der, Gageldonk-Lafeber RB van, Beest DE te, Koopmans M, Meijer A, Timen A, Swaan C, Dalhuijsen A, Hahné S, Hoek A van den, Teunis P, Sande MA van der, Wallinga J. Transmission of novel Influenza A(H1N1) in households with post-exposure antiviral prophylaxis. PLoS One. 2010 Jul 7;5(7):e11442.

Donker T, Boven M van, Ballegooijen WM van, Klooster TM van 't, Wielders CC, Wallinga J. Nowcasting pandemic influenza (H1N1) 2009 hospitalizations in the Netherlands. Submitted to Emerging Infectious Diseases (May 2010).

Gageldonk-Lafeber RB van, Hooiveld M, Meijer A, Donker T, Veldman-Ariesen M, Hoek W van der, Sande MA van der. The relative impact of 2009 pandemic Influenza A(H1N1) in the general population compared to seasonal influenza in the

Netherlands was most marked among 5-14 year olds. Submitted Influenza And Other Respiratory Viruses (July 2010).

Gageldonk-Lafeber RB van, Riesmeijer RM, Friesema IHM, Meijer A, Isken LD, Timen A, Sande MA van der. Case-based reported mortality associated with laboratory-confirmed A(H1N1) 2009 influenza virus infection in the Netherlands. Submitted to Eurosurveillance.

Goldstein E, Apolloni A, Lewis B, Miller JC, Macauley M, Eubank S, Lipsitch M, Wallinga J. Distribution of vaccine/antivirals and the 'least spread line' in a stratified population. J R Soc Interface. 2010 May 6;7(46):755-64.

Hahné S, Donker T, Meijer A, Timen A, Steenbergen J van, Osterhaus A, Sande M van der, Koopmans M, Wallinga J, Coutinho R; Dutch New Influenza A(H1N1)v Investigation Team. Epidemiology and control of Influenza A(H1N1)v in the Netherlands: the first 115 cases. Euro Surveill. 2009 Jul 9;14(27). pii: 19267.

Hanquet G, Damme P van, Brasseur D, Cuyper X de, Gregor S, Holmberg M, Martin R, Molnar Z, Pompa MG, Snacken R, Sande M van der, Van Ranst M, Wirz A, Neels P. Lessons learnt from pandemic A(H1N1) 2009 influenza vaccination. Highlights of a European workshop in Brussels (22 March 2010). Vaccine 20; in press.

Herfst S, Chutinimitkul S, Ye J, Wit E de, Munster VJ, Schrauwen EJ, Bestebroer TM, Jonges M, Meijer A, Koopmans M, Rimmelzwaan GF, Osterhaus AD, Perez DR, Fouchier RA. Introduction of virulence markers in PB2 of pandemic swine-origin influenza virus does not result in enhanced virulence or transmission. J Virol. 2010 Apr;84(8):3752-8.

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Appendix 1 List of abbreviations

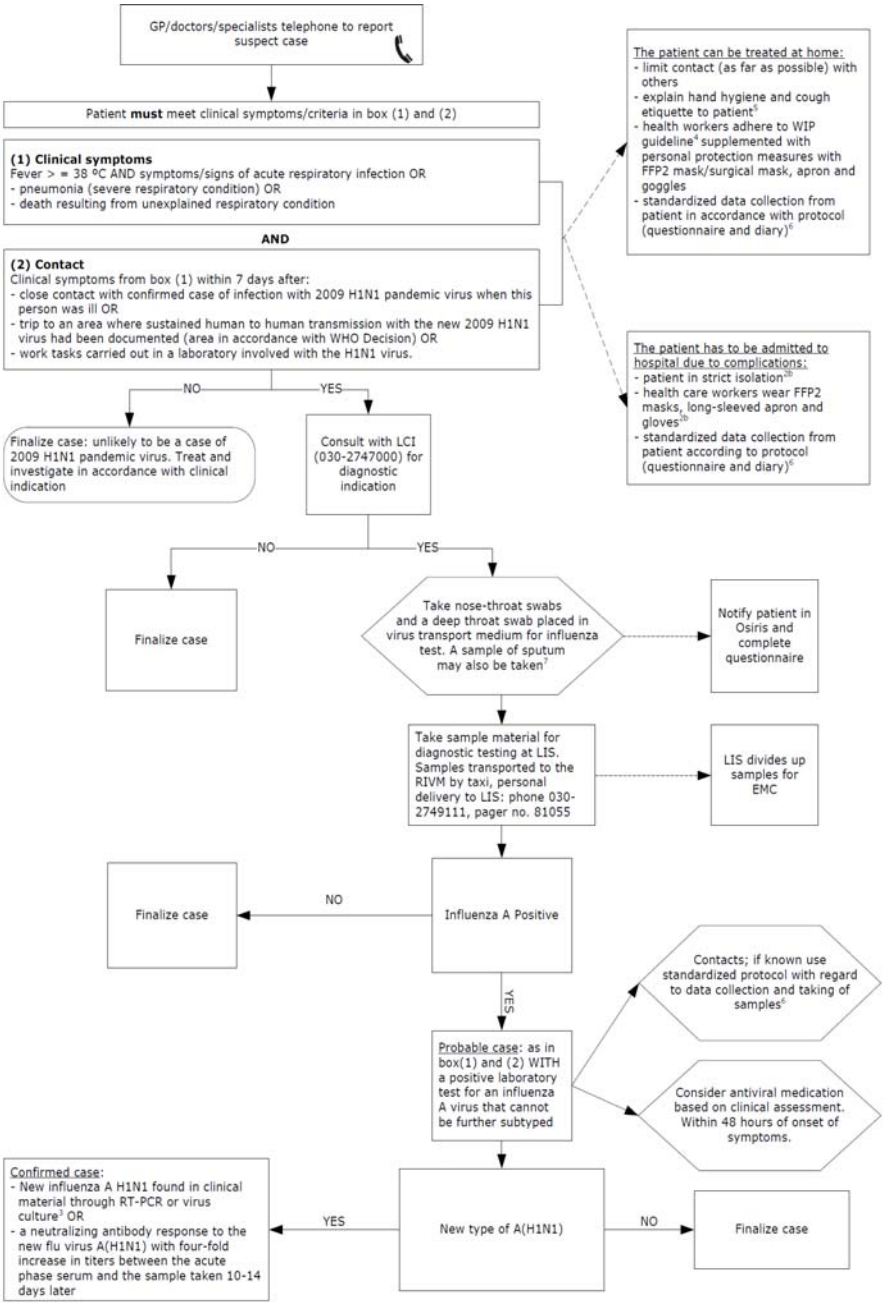
ACIP	Advisory Committee on Immunization Practices (US)
AMC	Academic/University Medical Centre
ARDS	Acute Respiratory Distress Syndrome
ARI	Acute Respiratory Infection
AVM	Antiviral agents/drugs
BAO	Administrative Consultative Committee on Infectious Diseases
BBA	Department of Policy, Operations Management and Advice
Boaborea	Umbrella organization for occupational health and reintegration
BSL	Biosafety level
BSN	National identification number
BTCB	VWS policy team for crisis containment
BuZa	Ministry of Foreign Affairs
BZK	Ministry of the Interior and Kingdom Relations
CBG	Medicines Evaluation Board
CBS	Statistics Netherlands
CDC	Centers for Disease Control and Prevention (US)
CFIA	Canadian Food Inspection Agency
CHMP	Committee for Medicinal Products for Human Use
CIb	Centre for Infectious Disease Control
COM	Committee of Diagnostic Microbiology
COM'er	Regional consultants medical microbiology
CvB	Centre for Population Screening
cVTV	Centre for Public Health Forecasting
ECDC	European Centre for Disease Prevention and Control
EFTA	European Free Trade Association
EISN	European Influenza Surveillance Network
EISS	European Influenza Surveillance Scheme
EL&I	Economic Affairs, Agriculture and Innovation
EMC	Erasmus Medical Centre Rotterdam
EMDD	Expert Meeting on Disease Detection
EMEA	European Medicines Agency
EPI	Department of Epidemiology and Surveillance
EQA	External Quality Assessment
ESCAIDE	European Scientific Conference on Applied Infectious Disease Epidemiology
EVM	European Vaccine Manufacturers
EWRS	Early Warning and Response System
FDA	Food and Drug Administration (US)
GD	Animal Health Service
GGD	Public Health Services
GGD NL	GGD Netherlands
GHOR	Medical Assistance Services for Accidents and Disasters
GIS	Geographic Information System
GR	Health Council
GSK	GlaxoSmithKline
HHS	Department of Health and Human Services (US)
HIS	GP Information System
HPA	Health Protection Agency (United Kingdom)
HPV	Human Papilloma Virus
HSC	Health Security Committee
ILI	Influenza-like illness
ICCB	Inter-departmental Committee for Crisis Management (formerly IBT)

ICU	Intensive Care Unit
IHR	International Health Regulations
ISI	Information Standards for Infectious Diseases (factsheet)
JGZ	Youth Health Care Service
KNMP	Royal Dutch Pharmaceutical Society
KNOV	Royal Dutch Organization of Midwives
Lareb	Dutch Pharmacovigilance Centre
LCI	National Coordinating Body for Infectious Disease Control
LCR	National Coordination Centre for Travellers
LHV	Dutch Society for General Practitioners
LIMS	Laboratory Information Management System
LINH	National Information Network for General Practice
LIS	Laboratory for Infectious Disease Diagnostics and Screening
LNV	Ministry of Agriculture, Nature and Food Quality
LZO	Laboratory for Zoonoses and Environmental Microbiology
MEC/METC	Medical Ethics (Review) Committee
MIDAS	Models of Infectious Disease Agent Study
MML	Medical Microbiology Laboratory
MMWR	Morbidity and Mortality Weekly Report (US)
NCvB	Netherlands Centre for Occupational Diseases
NFU	Dutch Federation of University Medical Centres
NHG	Dutch College of General Practitioners
NIAID	National Institute of Allergy and Infectious Diseases (US)
NIC	National Influenza Centre
NIVEL	Netherlands Institute for Health Services Research
NTvG	Netherlands Journal of Medicine
NVAVG	Netherlands Society of Physicians for Persons with Intellectual Disabilities
NVI	Netherlands Vaccine Institute
NVK	Dutch Society of Paediatrics
NVMM	Dutch Society for Medical Microbiology
NVOG	Dutch Society of Obstetrics and Gynaecology
NVZ	Dutch Hospitals Association
NZa	Dutch Healthcare Authority
OMT	Outbreak Management Team
PAHO	Pan American Health Organization
PHAC	Public Health Agency of Canada
PHE	Public Health Emergency
PICU	Paediatric Intensive Care Unit
RAC'er	Regional Consultants Communicable Disease Control
RCP	Regional Coordination Programmes
RIVM	National Institute for Public Health and the Environment
RIVM-com	RIVM Departments of Corporate Communication and CIb-Communication
RSV	Respiratory Synctial Virus
RVP	National Vaccination Programme
SAGE	Strategic Advisory Group of Experts on Immunization of the WHO
SARI	Severe Acute Respiratory Infection
SFK	Foundation for Pharmaceutical Statistics
SNIV	Surveillance Network for Infectious Diseases in Nursing Homes
SNPG	National Influenza Prevention Programme
TIS	Teratology Information Service
UMC	Academic Medical Centre
Verenso	Professional Organization for Geriatric Specialists
VIZ	Netherlands Association for Infectious Diseases
VWA	Food and Consumer Product Safety Authority
VWS	Ministry of Health, Welfare and Sport

WHO	World Health Organization
WIP	Dutch Working Party on Infection Prevention
WOGIZ	Working Party for Public Health Care and Infectious Diseases

Appendix 2 Algorithm for the management of suspect cases of 2009 H1N1 influenza[1]

On May 4, 2009, the algorithm for use by the regional GGDs for the management of patients with suspected 2009 H1N1 infection was circulated. The chart presents a clear overview of the measures that had to be taken by the regional GGDs. The chart was based on the procedures manual: *Part 2, Incidental Introduction of a New Human Influenza Virus in the Netherlands* drawn up by the LCI [8].



1. Flow chart in accordance with WHO Decision (with allowances for WHO changes), **2a.** See for measures the procedures manual *Incidental Introduction of a New Human Influenza Virus in the Netherlands,* section 2.3.2., **2b.** In accordance with WIP guideline on personal protective measures in hospitals (see www.wip.nl), **3.** The virus culture must be dealt with at BSL-3 level, **4.** WIP guideline for nursing homes, residential homes and home care, see section 'personal protective measures' (see www.wip.nl), **5.** See for measures the procedures manual *Incidental Introduction of a New Human Influenza Virus in the Netherlands,* section 2.4. **6.** Questionnaires on risk factors, diaries on exposure and clinical picture, taking virological serological samples is fully outlined in protocol. Data can be linked in Osiris, LINKS and Pandora (operational from week 20). **7.** See appendix VIa *Incidental Introduction of a New Human Influenza Virus in the Netherlands*

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