

**A CASE-CONTROL STUDY ON INFLUENZA A(H1N1)2009
VIRUS INFECTION IN THE FIRST FEW 100 (FF100)
CASES AND CLOSE CONTACTS:
RESULTS AND LESSONS LEARNED FROM THE NETHERLANDS**

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A(H1N1)2009 CONSORTIUM

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ABSTRACT

Background: Rapid collection of detailed data of the first few hundred (FF100) cases and their close contacts (exposed but healthy controls) was included in the comprehensive assessment of the Dutch pandemic preparedness plan. This enabled us to perform a case-control study, assessing patient characteristics and risk factors for experiencing a symptomatic influenza A(H1N1)2009 infection and providing insight into transmission. We set out to evaluate the FF100 approach in terms of the feasibility during the 2009 pandemic and the added value compared with alternative data sources available.

Methods: Cases and contacts were recruited using the national mandatory notification system and the Dutch sentinel influenza surveillance system. Contacts were considered as controls matched for exposure to influenza A(H1N1)2009 virus. Virological and serological sampling was scheduled at days 0, 5, 10 and 30. We assumed that persisting high titers in first and follow-up blood samples of controls indicated exposure to the same source as the case, and that seroconversion indicated secondary transmission. Both cases and controls were asked to complete a questionnaire, extracting information about demographics, medical history, and exposure to influenza A(H1N1)2009 virus. We assessed to what extent timely and novel data were generated compared to other available data sources.

Results: In May-December 2009, a total of 68 cases and 48 controls were included in the study. Underlying non-respiratory diseases were significantly more common among cases compared to controls ($OR_{adj}=9.7$; 95%CI: 1.6-57.9), while a protective effect was found for frequent (>8 times/day) hand washing ($OR_{adj}=0.4$; 95%CI: 0.2-0.9). Seroconversion was found for 7/30 controls (23%), and persisting high titers for 4/30 controls (13%). The labour-intensive study design resulted in slow and limited recruitment of cases and contacts.

Discussion: The findings of an increased risk for symptomatic infection in people with underlying non-respiratory disease, a protective effect of frequent hand washing and a secondary transmission rate of approximately 20% gave new insights in transmission risks and possible interventions for improved control. While our design resulted in novel findings, the FF100 approach lacked timeliness and power due to slow and limited recruitment. For future pandemics, we suggest to pool data from several countries, to enable collecting sufficient data in a relatively short period.

INTRODUCTION

Influenza A viruses have caused three major pandemics during the twentieth century: the Spanish flu virus A(H1N1) in 1918, the Asian flu virus A(H2N2) in 1957, and the Hong Kong flu virus A(H3N2) in 1968 [1-3]. Since 1997, emerging highly pathogenic avian influenza A viruses, particularly A(H5N1), have infected humans in several Asian and European countries. The worldwide increase in the incidence of influenza caused by avian influenza viruses, both in poultry and humans, introduced the potential for another influenza pandemic and the need for pandemic preparedness plans [4-8]. These preparedness plans are based on enhanced (pandemic) influenza surveillance systems for data collection, and can generally be divided in three parts. The first part is the early detection of sustained human-to-human transmission of an influenza virus with pandemic potential. The second part is the comprehensive assessment of the first few hundred cases to characterise clinical, virological and epidemiological features and for risk factor information, and the final part is monitoring the course of the pandemic at a national level.

Despite the continuing threat of avian influenza viruses, the first official influenza pandemic in the 21st century was caused by the so-called influenza A(H1N1)2009 virus. In April 2009, this swine-origin influenza virus was identified as the cause of outbreaks of febrile respiratory infections in Mexico and the United States, and in June 2009 the World Health Organization (WHO) declared the start of the pandemic [9,10]. In the Netherlands, as elsewhere, initial rapid assessments of the impact of this new influenza virus on the human population have been based on case-studies of the first notified laboratory-confirmed cases [11,12]. These studies provided vital information to guide management, but more standardised and detailed information was still needed to guide control activities and for communication with the general public and the media. The Dutch pandemic preparedness plan included a generic study protocol and questionnaires to rapidly collect detailed epidemiological, clinical, virological and immunological data of a limited number of patients and their close contacts. The design of this First Few Hundred (FF100) cases and contacts approach enabled a case-control study, aiming at identifying patient characteristics and risk factors for experiencing a symptomatic influenza A(H1N1)2009 infection in the general Dutch population, and made it possible to get insight into the transmission of the influenza virus.

This report summarises the findings from the case-control study with respect to risk factors and transmission. Furthermore, the FF100 cases and contacts approach is discussed in terms of the feasibility during the 2009 pandemic and the added value compared with alternative data sources available.

METHODS

STUDY DESIGN

A comprehensive generic study protocol for detailed data collection was written following the 2003 outbreak of influenza A(H7N7) among poultry in the Netherlands [13,14], and approved beforehand by the Medical Ethical Review Committee of the University Medical Centre Utrecht in 2007. In May 2009, the protocol was adapted to the situation of the pandemic threat at that time, and again approved by the same Medical Ethical Review Committee. The study started in June 2009, and was performed by the Centre for Infectious Disease Control (CIb) of the National Institute for Public Health and the Environment (RIVM), in collaboration with Municipal Health Services (MHS), a network of academic medical centres and the network of general practitioners (GP) from the Continuous Morbidity Registration Sentinel General Practice Network of The Netherlands Institute for Health Services Research (NIVEL).

CASES AND CONTROLS

Up to the 15th of August 2009, cases were recruited using the national mandatory notification system. Cases were defined as persons with a clinical diagnosis of influenza-like illness (ILI) and a laboratory-confirmed influenza A(H1N1)2009 virus infection. As soon as possible upon virological confirmation [15,16] of an influenza A(H1N1)2009 virus infection in a patient, the local MHS, which notified the patient, was contacted by the CIb pandemic influenza research team. The MHS informed the patient about the study and asked if there were asymptomatic close contacts willing to participate as controls in the study. A contact was defined as a person who had close contact with the case in the early stage of infection, and who had no symptoms of ILI at the time of inclusion in the study. Controls developing symptoms of ILI during the period of follow-up were maintained

as controls according to the study design. These contacts were considered as controls matched for exposure to influenza A(H1N1)2009 virus. From the 15th of August 2009, only hospitalised or deceased patients with a laboratory-confirmed influenza A(H1N1)2009 virus infection were notifiable [12], hampering the further inclusion of cases via the MHS. Therefore, from the 15th of August, patients from the Dutch sentinel influenza surveillance system with a laboratory-confirmed influenza A(H1N1)2009 infection were also approached to participate in the study. The national influenza surveillance system exists for over 40 years and is a collaboration between the CIb of the RIVM, NIVEL, and the Erasmus University of Rotterdam [17,18]. The GP informed the patient about the study and recruited contacts willing to participate as controls. To include also patients with severe disease, patients with a laboratory-confirmed influenza A(H1N1)2009 infection hospitalised in academic centres, as well as their close contacts, were approached to participate in the study.

DATA COLLECTION

After consenting, both cases and controls were visited by a research nurse at day 0 (within 8 days from the onset of disease). During this first visit the study objectives were further clarified, the case and control information was handed over, and written informed consent was obtained from both the case and control(s). As shown in the schedule, data collection was carried out at days 0, 5, 10 and 30. From the 15th of August onwards, the first GP consultation was counted as the day 0-visit for cases and the first home visit for controls was scheduled at day 5. For cases as well as controls, the number and type of samples taken before and after the 15th of August were the same, with the exception of an extra blood sample (finger prick) for cases taken at the GP visit. The same schedule was also applied for hospitalised cases and their controls. During hospitalisation, the study was carried out in the hospital by the attending physician. After discharge, the remaining home visits were taken over by a research nurse.

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Schedule. Study schedule of the case-control study in the period before and after the change of notification criteria for influenza A(H1N1)2009 influenza virus infection at the 15th of August 2009, the Netherlands.

		Day 0	Day 5 range [4-6]	Day 10 range [9-11]	Day 30 range [28-35]
Up to 15 august 2009		visit1	visit2	visit3	visit4
case patients	nose- and throat swab*		X	X	
	venipuncture	X [^]		X	X
control subjects	nose- and throat swab	X			
	venipuncture	X		X	X
From 15 august 2009		GP visit	visit1	visit2	visit3
case patients	nose- and throat swab	X [^]	X	X	
	venipuncture	X [^] #	X	X	X
control subjects	nose- and throat swab		X		
	venipuncture		X	X	X

* The diagnostic nose- and throat swab on which the patients were included in the study was taken by the physician of the municipal health service and is not entered in the schedule

[^] For hospitalised cases the first visits, until the moment of discharge, were scheduled in hospital

The GP took a finger prick instead of a venipuncture

Both cases and controls were asked to complete a detailed questionnaire. This questionnaire included questions about demographics, medical history, use of medication, exposure to influenza A(H1N1)2009 virus, symptoms of the current episode, and hygiene aspects. Parents or guardians were asked to complete questionnaires for their young children.

LABORATORY METHODS

REAL-TIME RT-PCR

For rapid diagnostics of the pandemic influenza A(H1N1)2009 virus, real-time RT-PCR for general detection of influenza virus type A and B was combined with identification of the pandemic influenza A(H1N1)2009 virus as described previously [15]. Briefly, nucleic acid was purified from the combined nose and throat swabs using a MagnaPure LC system with the MagnaPure LC total nucleic acid isolation kit (Roche Diagnostics, Almere, the Netherlands). qRT-PCR was performed on a LightCycler 480 (Roche Diagnostics). qRT-PCR diagnostics was initially done using the Taqman Master kit for two-step qRT-PCR (Roche Diagnostics, Almere, the

Netherlands), replaced during the 2009 A(H1N1) pandemic by the TaqMan EZ RT-PCR core reagents kit for one-step qRT-PCR (Applied Biosystems, Nieuwerkerk aan den IJssel, the Netherlands).

SEROLOGY

Venous blood was collected *lege artis*. Blood was delivered by the research nurse or returned by regular overnight mail to the laboratory of the RIVM, and serum was stored at -20°C until analysis. A hemagglutination inhibition (HI) assay was performed using A/California/7/2009 (H1N1; vaccine strain X-181) influenza virus as hemagglutinating antigen. Turkey red blood cells were used as indicator cells. Serum samples were pre-treated with cholera filtrate receptor-destroying enzyme to remove autoagglutinating activity of the sera. After cholera filtrate treatment, some samples showed remaining auto-agglutination. These samples were further pre-treated by adsorption with packed turkey red blood cells. The pre-treated samples were tested in duplicate at an initial dilution of 1/20 in serial two-fold dilutions. The international standard antiserum (pooled human serum against A/California/7/2009 (vaccine strain X-179A) obtained from the NIBSC, catalogue number 09/194 (NIBSC HPA. Influenza reagent candidate international standard for antibody to influenza H1N1pdm virus. NIBSC code: 09/194. Version 2.0, Dated 07/04/2010)) was used to convert titres to the international standard. Titres were expressed as the reciprocal of the highest dilution of serum that fully prevented hemagglutination. For calculation purposes, titres for specimens that did not show any hemagglutination inhibition were set at 5. For each sample, the geometric mean of the duplicate standardised titres was used.

Seroconversion was defined as a change in titre from no hemagglutination inhibition to a titre $\geq 1:40$, or as having a four-fold or greater rise in titres between two successive samples.

STATISTICAL ANALYSES

Descriptive statistics were calculated, results of categorical variables are presented as percentages and continuous variables as median with range. Multivariate logistic regression analysis was used to examine whether patient characteristics and/or potential risk factors were associated with a laboratory-confirmed symptomatic infection. The dependent variable was symptomatic disease (i.e. being a case or

control). Variables with a P-value ≤ 0.10 in the univariate model were included in the multivariate model. Backward selection was used to identify covariates that were independently associated with symptomatic disease. Significant odds ratios (OR) were presented with 95% confidence intervals (CI).

Insight in transmission was obtained by studying the serology results for controls. These analyses were restricted to controls of whom at least two blood samples were available. Persisting high titers ($\geq 1/40$) in the first and following blood samples were considered as a proxy for exposition to the same source as the case, while seroconversion was considered as a proxy for secondary transmission whereby the cases acts as source for the control.

With respect to the feasibility of our study design during the 2009 pandemic, we assessed the number and timing of inclusion of patients willing to participate in the study versus the total number of notified influenza A(H1N1)2009 virus infections in relation to the timing of notifications. Furthermore, the age distribution of included patients was compared with that of the notified patients. The added value of the used approach was explored by comparing the findings of the case-control study with alternative data sources. Statistical analyses were performed using SAS version 9.2 (SAS Institute).

RESULTS

Between June and December 2009 a total of 76 of 120 invited patients were willing to participate in the study (63%). Written informed consent and a completed questionnaire were received for 68 of these cases, as well as for 48 controls. The response rate for controls could not be assessed, since no information about the number of approached controls was available. Next to the questionnaire, at least one combined nose and throat swab was available for all cases and at least one blood sample for 32 cases (47%). For the controls these numbers were 34 (71%) and 33 (69%), respectively. The age distribution of cases and controls is shown in figure 1.

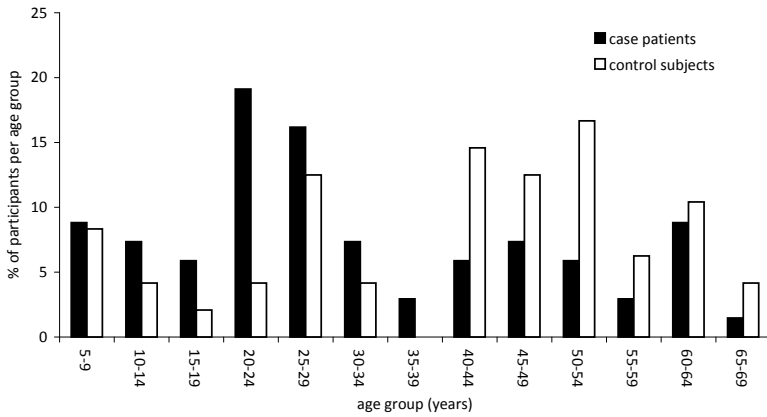


Figure 1. Age distribution of cases and controls of the case-control study during the influenza A(H1N1)2009 pandemic in the Netherlands, 2009.

The median age of cases (26 years, range: 5-67 years) was significantly lower than that of controls (45 years, range: 7-67 years). Underlying lung disorders, including asthma, COPD, and cystic fibrosis, were reported by 28% of the cases and 25% of the controls ($p=0.7$). Underlying non-respiratory diseases, including various disorders like cardiovascular disorders, immunological disorders and diabetes mellitus, were reported by 18% of the cases and 5% of the controls ($p=0.04$). For 65% of the controls contact with a case was reported to be within the household, and for 6% of the controls this contact was with more distant relatives (unknown for 14 controls (29%)). More than half of the cases reported a recent contact with a person probably infected with influenza A(H1N1)2009 virus.

CLINICAL SYMPTOMS

Clinical symptoms reported in the questionnaire by cases with a laboratory-confirmed influenza A(H1N1)2009 virus infection, are shown in table 1. Cough was the most commonly reported symptom (78%), followed by fever (72%), fatigue (69%) and headache (69%).

Table 1. Clinical symptoms of cases with a laboratory-confirmed influenza A(H1N1)2009 virus infection included in the case-control study during the influenza pandemic in the Netherlands, 2009.

Clinical symptoms [*]	n	(%)
Cough	38	77.6
Fever ^{**}	31	72.1
Fatigue	34	69.4
Headache	33	67.3
Sore throat	25	51.0
Mucus	24	49.0
Myalgia	22	44.9
Rhinitis	20	40.8
Shortness of breath	18	36.7
Nausea	11	22.4
Diarrhea	10	20.4
Joint complaints	10	20.4
Painful breathing	7	14.3

^{*} Symptoms were reported by 49 of the 68 patients with a laboratory-confirmed influenza A(H1N1)2009 virus infection.

^{**} Information about fever was available for a total of 43 patients with a laboratory-confirmed A(H1N1)2009 influenza virus infection

RISK FACTORS

Cases and controls were compared with respect to reported medical history, smoking, antiviral treatment, seasonal influenza vaccination status, and current hygiene aspects to assess which variables were independently associated with symptomatic disease. Multivariate logistic regression analyses, adjusted for age and gender, showed that underlying non-respiratory diseases (including cardiovascular disorders, immunological disorders and diabetes mellitus) were significantly more common among cases compared to controls (OR=9.7; 95%CI: 1.6-57.9). Next to this, a protective effect of frequent (≥ 8 times a day) hand washing was found (OR=0.37; 95%CI: 0.15-0.90).

TRANSMISSION

Seroconversion was found for seven of the 30 controls (23%), of whom at least two blood samples (minimal 8 days apart), were available. For three of these seven controls the PCR of the combined nose and throat swab, taken at the inclusion in the study, was positive.

Persisting high titers in the first and following blood samples were found for four of the 30 controls (13%). For one of them the PCR, taken at the inclusion in the study, was positive. For a total of 19 controls (63%), no serological response was found.

FF100 CASES AND CONTACTS APPROACH

Inclusion of the required number of cases and contacts during the period of influenza activity in the Netherlands lagged behind the notified cases. By the time the first hundred patients were notified, two cases were recruited, and by the time 200 patients were notified, 14 cases were recruited. Figure 2 shows the number of included patients willing to participate in relation to the number of notified patients.

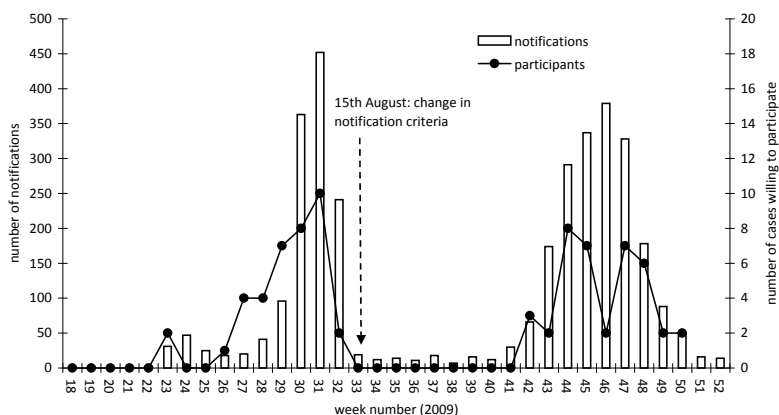


Figure 2. Number of notified patients and number of cases willing to participate in the case-control study during the influenza A(H1N1)2009 pandemic in the Netherlands, 2009.

About 50% of the cases were included via the MHS before the 15th of August. The remaining 50% was included via the GPs from the NIVEL network. Three of the participating cases were admitted to hospital, of which two were included through the participating academic medical centres. The inclusion of hospitalised cases could only start a median of 153 days after the approval of the baseline

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protocol, because it was necessary to obtain approval of the study protocol by the Medical Ethical Review Committees of the individual academic centres.

All age groups were represented in the case-control study (figure 1), and the age distribution corresponds to that of the first 115 laboratory-confirmed cases in the Netherlands [11].

The control/case ratio in the study is 0.7 (48/68), indicating we included less than one control per case. The inclusion of children as control was in particular difficult, as indicated by the significantly higher median age of controls compared to cases.

DISCUSSION

The Dutch FF100 case-control study confirmed that disease caused by infection with influenza A(H1N1)2009 virus was relatively mild, and at the same time observed an increased risk of symptomatic infection among those with non-respiratory underlying conditions while frequent hand washing was found to be protective. In addition, serological results indicated that nearly a quarter of the exposed contacts had evidence of secondary transmission. However, the labour-intensive design was logistically extremely challenging during times of intense work pressure, resulting in slow and limited recruitment. Despite intensive preparedness planning, the added value of the comprehensive assessment of the FF100 cases and contacts during the 2009 influenza pandemic in the Netherlands was restricted due to limited number of participants underlying the novel observations and the delay in recruitment of both cases and controls.

Respiratory and systemic symptoms were most common in our study population of mainly ambulatory patients, but also gastrointestinal symptoms were reported by more than one fifth of the patients. The clinical presentation was generally mild, resembling seasonal influenza, which is in line with other studies [9,19-23]. The results of our study suggest an increased risk for symptomatic infection in patients with underlying non-respiratory diseases. This is in contrast with several other studies observing that established risk factors for complications of seasonal influenza were also associated with severe illness from influenza A(H1N1)2009 infection [12,24-28]. Although selection bias cannot be excluded, the mechanism of such bias is not clear, as the GP would be the physician to consult for patients with underlying lung diseases as well. However, inclusion of cases by the GP was restricted to the period from the 15th of August onwards. Before that date, all patients with a laboratory-confirmed influenza A(H1N1)2009 virus infection had to be notified by the MHS and were eligible for inclusion in the study. Another explanation might be that our findings were based on patients with relatively mild diseases, while other studies mainly focused on (hospitalised) patients with severe disease. Frequent hand washing appeared to have a protective effect on symptomatic infection. Assuming that daily hand washing frequency is a proxy of the hand hygiene in general, this finding suggests that hand hygiene may reduce the transmission of pandemic influenza virus. This is in agreement with recent studies suggesting that hand hygiene prevents transmission of influenza

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A(H1N1)2009 virus in households and crowded communities [29-31]. However, heightened attention to hygienic behaviour for controls facing a diseased relative or friend may have caused recall bias in the present study. The results of these analyses could have been influenced by differences in the severity of disease between extramural and hospitalised patients, but exclusion of hospitalised patients led to similar results.

Based on serological responses of the controls included in our study, the secondary transmission rate was over 20%. This is in line with Cowling et al. [21], reporting a fourfold or greater rise in antibody titer in about one fifth of the household contacts, although no distinction was made between pandemic and seasonal influenza virus in that study. The persistently high titers found in four controls in our study, might indicate that they had been exposed to the same source as their case. For at least one control, this assumption is supported by a positive PCR at inclusion in the study, although a cross-reactive response cannot be excluded.

The addition of the FF100 cases and contact approach to the comprehensive assessment of the Dutch pandemic preparedness plan was based on the experiences of the 2003 outbreak of influenza A(H7N7) among poultry in the Netherlands [13,14]. Rapid and structured collection of detailed epidemiological, clinical, virological and immunological data appeared to be essential for the management of control activities and for communication. The inclusion of both cases with relatively mild symptomatic infection and of close contacts is a strength of the FF100 cases and contacts approach. Most studies on influenza A(H1N1)2009 virus so far concern case-series, mainly including severe cases and most studies on risk factors focused on a serious outcome of disease caused by influenza A(H1N1)2009 infection [12,24-28,32,33]. Moreover, the inclusion of contacts improved the insight in both risk factors for symptomatic infection in the general Dutch population and in the transmission of pandemic influenza A(H1N1)2009 virus to close contacts.

Nevertheless, the course of the 2009 pandemic and the resulting workload made it impossible to include the intended first few hundred cases and contacts in a limited period, which is a substantial limitation of our study. Since the influenza A(H1N1)2009 virus had already spread internationally before it was recognised, the implementation of containment and mitigation measures was practically impossible, resulting in a rapid increase of the number of cases worldwide [34]. Following the restriction of the mandatory notification in the Netherlands on the

15th of August 2009 [12], only a relatively small number of cases and controls were available for inclusion in the study. Moreover, the public perception of the pandemic changed when it became clear that the majority of patients developed mild disease, and therefore patients were less willing to participate in the study. This is in line with findings in the FF100 cases project in the UK. McLean et al. [20] also showed that initially almost all laboratory-confirmed cases were included in the 'first few 100 project' in the UK, but as the case numbers began to increase, the proportion of cases included also decreased. This might have introduced some additional selection bias but this is unlikely to have influenced our results.

We acknowledge there are some further limitations to our design. First, questionnaire data were used to report patient characteristics and to measure exposure to potential risk factors. This could be less reliable compared with observational data. Moreover, heightened attention to the cause of their complaints by cases may have caused recall bias. Secondly, we cannot rule out the possibility that controls were in the incubation period for infection, even though they had no respiratory complaints at the moment of inclusion. This might have diluted the investigated relations between symptomatic disease and patient characteristics as well as potential risk factors.

Despite the slow and limited recruitment, the FF100 cases and contact approach is well suited for rapid and detailed collection of epidemiological, clinical, virological and immunological data, and is a necessary addition to case-based data. This is also shown by the FF100 cases project in the UK [20]. The UK was one of the first European countries affected and experienced a substantial first wave in spring and summer 2009. Their FF100 cases project was rapidly established and captured information on almost 400 of the first UK cases in the first 7 weeks of the pandemic [20].

For future pandemics, we therefore suggest that several countries share the same comprehensive baseline study protocol to rapidly collect detailed epidemiological, clinical, virological and immunological data of the first few hundred cases as well as their close contacts. This will facilitate the possibility to pool the data, and therefore increase the number of both cases and close contacts resulting in more timely data and more power to strengthen novel findings. Similar European projects are already initiated, like EURO-MOMO monitoring the excess mortality and ECDC I-MOVE monitoring the influenza vaccine effectiveness [35-38]. This will require revision and harmonisation of the pandemic preparedness plans, which has to be elaborated in the inter pandemic period.

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In conclusion, the labour-intensive design of the FF100 cases and contact approach resulted in a limited recruitment, however the findings of our study were supplementary to those of case-based studies and important to guide control activities and for communication. Our study showed an increased risk for symptomatic infection in cases with underlying non-respiratory disease, a protective effect of frequent hand washing and a secondary transmission rate of about 20%. To increase timeliness and power during future pandemics we suggest to pool the epidemiological, clinical, virological and immunological data for both the first few hundred cases and their close contacts of several countries, to make it possible to collect the required data in a relatively short time period.

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