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Public health implications of using various case definitions in The Netherlands during the worldwide SARS outbreak

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ABSTRACT

This study analysed the consequences of deviation from the WHO case definition for the assessment of patients with suspected severe acute respiratory syndrome (SARS) in The Netherlands during 2003. Between 17 March and 7 July 2003, as a result of dilemmas in balancing sensitivity and specificity, five different case definitions were used. The patients referred for SARS assessment were analysed from a public health perspective. None of the patients referred had SARS, based on serological and virological criteria. Nevertheless, all 72 patients required thorough assessment and, depending on the results of the assessment, institution of appropriate prevention and control measures. Changing case definitions caused confusion in classifying cases. A centralised assessment of the reported cases by a team with clinical and public health expertise (epidemiological and geographical risk assessment) is a practical solution for addressing differences in applying case definitions. The burden of managing non-cases is an important issue when allocating public health resources, and should be taken into account during the preparation phase, rather than during an outbreak. This applies not only to SARS, but also to other public health threats, such as pandemic influenza or a bioterrorist episode.

Keywords Assessment, case definition, management, public health threats, risk assessment, SARS

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INTRODUCTION

Severe acute respiratory syndrome (SARS) confronted communicable disease professionals with new dilemmas concerning the assessment and management of suspect cases, because of an initial lack of knowledge of the pathogen, its transmission route, its incubation period and its clinical presentations. The sense of urgency increased with evidence that the disease could spread easily and that the clinical course could be severe [1–4]. Following the WHO global alert on 12 March 2003 and the WHO travel advisory notice on 15 March 2003, countries worldwide started reporting cases [5,6]. In May 2003, the WHO revised the case definitions of SARS [7], based on knowledge of the disease available at that time. Early studies in 2003 showed a low sensitivity (26%) when using the WHO criteria for clinical assessment of patients before admission to a SARS clinic in a region with extensive local transmission [8]. A comparable low sensitivity (27%) and a much lower positive predictive value were found when screening patients before admission to a general hospital in Singapore [9]. In the designated screening centre for evaluation of possible SARS cases in Singapore, the WHO case definitions were found to be helpful at initial assessment, despite an under-triage of 0.3% [10]. To address the low sensitivity of the WHO criteria, researchers from Hong Kong developed a clinical prediction rule for the emergency department [11].

Case definitions are used for different purposes, i.e., surveillance, clinical care, research and service provision [12]. Their benefits and limita-

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tions in practice depend on their purpose, the context in which they are used, and the skills of the user. When formulating a case definition, balancing sensitivity and specificity is crucial [13]. The initial emergence and spread of SARS in the absence of specific diagnostic tests required that physicians and public health authorities worldwide formulate a set of criteria for separating suspected or probable cases from non-cases. This report describes the background, and the choices made with respect to classification and management, of patients referred for SARS assessment in The Netherlands. The consequences of the use of different case definitions for the reporting behaviour, patient management and evaluation of public health interventions are highlighted. None of the cases met the criteria for reporting to the WHO according to the case definitions in force at the time in The Netherlands. All cases were re-evaluated on the basis of the latest case definition from the WHO (1 May 2003) [7], and differences with important public health consequences were revealed.

MATERIALS AND METHODS

Case definitions for suspect and probable cases of SARS in The Netherlands

On 15 March 2003, the WHO issued a case definition for SARS. The first Dutch case definition, dating from 17 March 2003 (Table 1), for surveillance purposes and comprehensive clinical assessment, required obligatory radiographical evidence of lung infiltrates consistent with pneumonia, and well-defined epidemiological criteria for exposure (i.e., close contact with an individual with severe respiratory disease in the affected areas during the previous 10 days). This more specific case definition was issued to avoid considering SARS in the differential diagnosis of the expected large number of patients with acute respiratory infections at a time when the incidence of mild (common) respiratory disease in travellers was high and the influenza season was ongoing. General practitioners and clinicians were asked to report suspect cases on a voluntary basis to the Dutch Public Health Services. On 1 April 2003, mandatory SARS notification was introduced. The Public Health Services were asked to consult the National Co-ordination Centre for Outbreak Management (LCI) for an assessment of SARS probability. In the following weeks, four subsequent case definitions followed in which, gradually, sensitivity increased (Table 1) at the expense of specificity. The criteria for case definitions and notification were evaluated on each occasion by members of the Outbreak Management Team, who were responsible for issuing scientific advice. Major factors in balancing sensitivity and specificity were the severity of the clinical course, the frequency of local transmission in affected areas, and the level of contact with potentially infected individuals. On 10 June 2003, the WHO case definition for a suspect case (revised on 1 May 2003) was also adopted in The Netherlands for reporting patients for SARS assessment.

Cases

A retrospective descriptive analysis of the cases that were reported for SARS assessment in The Netherlands during the period 17 March to 7 July 2003 was conducted. Cases from two datasets were used. One dataset included the cases referred by regional public health physicians to the LCI. The second source was the dataset from the SARS reference laboratory in The Netherlands (Department of Virology, Erasmus MC Rotterdam), to which clinical specimens were sent. These cases were referred for SARS assessment on the basis of their clinical status, travel-associated risk and/or contact with suspect/probable SARS cases. The referral by the clinician/public physician was compared retrospectively with the assessment on the basis of the Dutch case definition at the time of submission, and with a reassessment on the basis of the WHO case definition issued on 1 May 2003. The risk ratio (RR) for being a suspect case was calculated by comparing the referral of the case by the clinician with the first assessment (RR1), the referral with the reassessment based on the WHO definition (1 May 2003) (RR2), and the first assessment with the reassessment (RR3). The data sources were compared using a capture–recapture method [14]. The same classification of cases was used for both data sources. Cases common in both data sources were identified using date of birth, date of onset, gender and city of residence.

Laboratory methods

Bacteriological cultures were performed on respiratory specimens in the referring hospitals. In the reference laboratory, serological testing for antibodies against SARS-coronavirus

Table 1. Criteria for the definition of cases of SARS in The Netherlands during 2003

Case definition (date)	Fever >38°C	Cough and breathing difficulty	Contact with patient with severe respiratory disease (in SARS area)	Travel to or residence in known SARS area	Contact with SARS patient outside affected area	Radiographical evidence of lung infiltrates (pneumonia)
1 (17 March)	+	+	+[a]	–	–	+
2 (1 April)	+	+	+[b]	–	–	–
3 (9 April)	+	+	+[c] or	+[d]	–	+
4 (2 May)	+	+	+[c] or	+[d] or	+	+
5 (10 June)	+	+	+ or	+ or	+	–

+, obligatory criterion; –, not an obligatory criterion for SARS assessment and notification.
[a]Hong Kong, Guangdong, Hanoi (Vietnam).
[b]Hong Kong, Guangdong, Hanoi (Vietnam) + China (Beijing, Shanxi), Taiwan, Singapore, Toronto and other affected areas with local transmission.
[c]In areas with local transmission, but without travel advice (Hong Kong and Guangdong thus not included).
[d]Areas with a travel advice at that time.

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(SARS-CoV) was carried out, and virus culture was performed in a category 3 biological safety laboratory facility, where the samples were also prepared for PCR testing.

Serology

Acute sera and, where possible, convalescent sera were tested for the presence of antibodies against SARS-CoV. The method used was an indirect immunofluorescence assay in which SARS-CoV-infected Vero 118 cells that had developed a cytopathic effect were used to coat microscope slides. Serum was diluted in serial two-fold steps from 1:10 to 1:40 in phosphate-buffered saline. After incubation with dilutions of the serum for 30 min at 37°C, the slides were washed with phosphate-buffered saline and incubated with rabbit anti-human IgG, IgA and IgM conjugated with fluorescein thiocyanate (Dako, Heverlee, Belgium). After washing and drying, the slides were examined with a fluorescence microscope [15]. The titre was defined as the highest dilution giving a 1+ or 2+ reaction.

Virus culture

Nose, throat and sputum specimens were tested specifically for respiratory viruses, including influenza A and B viruses, human respiratory syncytial virus, human parainfluenza virus types 1–4, adenovirus, human metapneumovirus and rhinovirus. Routine virological tests for respiratory pathogens were performed by a combination of virus isolation in cell cultures and immunofluorescence [16]. Virus isolation procedures for SARS-CoV were performed following inoculation of specimens on Vero 118 cells, a subclone from Vero 6 cells, human embryonic lung fibroblasts and tertiary monkey kidney cells. The presence of virus was confirmed by immunofluorescence, RT-PCR, or both.

PCR testing

Virus nucleic acid was purified using the Magna Pure LC automated nucleic acid isolation system (Roche Diagnostics, Mannheim, Germany). Swabs, bronchoalveolar lavages and sputum samples were processed with the Magna Pure LC Total nucleic acid serum plasma blood isolation kit. The presence of SARS-CoV RNA was assessed on an ABI Prism 7700 using the EZ rTtH RNA amplification kit (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) [15]. RT-PCR with primers and a probe specific for the nucleoprotein gene of SARS-CoV was used, as such an assay may be more sensitive than RT-PCRs based on the polymerase gene [15,17]. Specimens from the respiratory tract were also monitored for influenza A and B viruses, human respiratory syncytial viruses A and B, rhinoviruses, coronaviruses (OC43 and 229E) and human metapneumovirus, using essentially the same methods with specific primers [18,19].

RESULTS

Descriptive analysis

Between 17 March and 7 July 2003, 72 patients (43 males and 29 females) were referred for further SARS assessment. The LCI was consulted for 51 patients (source A), and the reference laboratory for 37 patients (source B). Sixteen patients were reported to both the LCI and the reference laboratory. Patients referred for SARS assessment to the LCI (source A) were referred mainly by public health officers (49/51), while clinicians referred suspect patients directly to the reference laboratory (35/37).

The date of onset of illness was known for 55 patients. The time between onset and referral varied from 0 to 40 days, with a mean of 4.5 (median 3) days. Same or next-day referral occurred for one-third of the patients. Three patients were referred ≥2 weeks after the onset of illness, with a maximum of 40 days (one case). The distributions of the clinical and epidemiological criteria for SARS among the referred patients are listed in Table 2. The patients with no history of travel to a SARS-affected area had travelled to other countries in south-east Asia. Six patients had no history of travel, but fulfilled, according to the physician, at least one clinical criterion for SARS, and had a risk of exposure in The Netherlands through close contact with travellers from affected areas.

Assessment and reassessment of presentations by general practitioners and clinicians

As presented, there were 52 (72.2%; 95% CI 60.4–82.1%) suspect cases and 20 (27.8%; 95% CI 17.9–39.6%) cases that were not suspect, but which had an indication for further assessment. The category 'not suspect with an indication for further assessment' included cases in which not all the criteria for classification as a SARS suspect case were met,

Table 2. Distribution of the criteria for the SARS case definition among cases referred for SARS assessment (n = 72)

Criteria	Number (%) n = 72	95% CI
Respiratory illness	53 (71)	61.9–83.3
Fever	49 (68)	56–78.6
Travel-associated risk	46 (64)	52.8–75.3
Close contact with individuals from affected areas	17 (23)	13.2–37.7
Pneumonia	11 (19.3)	10–31.9
Diarrhoea	4 (5.6)	1.5–13.6
Fever and travel-associated risk	28 (38.8)	27.8–50.2
Respiratory disease and travel-associated risk	29 (40.2)	28.9–51.5
Respiratory disease and fever	42 (58.3)	46.9–69.9
Respiratory disease, fever and travel-associated risk	25 (34)	23.3–45.2

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but in which the reporting physician could not rule out SARS without further assessment. Suspect cases were divided equally between males and females.

The assessment of the cases on the basis of the Dutch case definition in force at the time was compared with a retrospective reassessment on the basis of the WHO case definition of 1 May 2003 (Table 3). There was no significant difference between the risk of being a suspect/probable case at presentation vs. the risk following reassessment based on the WHO case definition (p 0.14), but there was a significant difference between the risk of being a suspect case at presentation and the risk in the first assessment based on the more precise case definition (RR1 1.46; $p < 0.05$ by Fisher's exact test) used at that time in The Netherlands. The risk of being a suspect case was significantly higher in the reassessment than in the first assessment when the more specific case definition was used (RR3 = 4.5; $p < 0.001$ by Fisher's exact test).

Laboratory outcomes

Virological investigations were performed on 37 patients, who presented as 33 suspect and four not-suspect cases. The same cases were categorised at the first assessment as seven suspect and 30 not-suspect. According to the WHO case definition used in the retrospective reassessment, the cases would have been divided into 12 suspect, 24 not-suspect and one probable. Antibodies to SARS-CoV were not detected in any of the acute sera. Convalescent sera from six patients were also tested for antibodies to SARS-CoV, but all were negative. Virus culture and RT-PCR testing for SARS on respiratory samples (16 patients) were also negative. Other viruses were detected in nine patients: influenza A in four, influenza B in one, rhinovirus in two, adenovirus in one and cytomegalovirus in one.

Table 3. Comparison of cases on the basis of the first assessment (based on the current Dutch case definition) and the retrospective reassessment (based on the WHO case definition)

	Retrospective reassessment			
First assessment	Not-suspect	Suspect	Probable	Total
Not-suspect	49	14	0	63
Suspect	0	7	2	9
Probable	0	0	0	0
Total	49	21	2	72

Case management

Six patients were put in strict hospital isolation [20] and seven were isolated at home until the laboratory results or the clinical course of the patient ruled out suspicion of SARS. Droplet and contact isolation precautions were advised for patients in home isolation. Unprotected carers and contacts of these patients were traced, and the intensity of their exposure was assessed. When necessary, body temperatures were monitored. For eight patients, restriction of contacts outside the household was advised in order to increase their social distance (e.g., by exclusion from work and social events), but isolation was not considered to be necessary. All suspect cases were given advice on respiratory hygiene and contact precautions.

DISCUSSION

Mandatory notification of SARS was introduced in The Netherlands a few weeks after the worldwide alert, and proved to be a valuable instrument, since most (78.2%) of the suspect patients were reported within 5 days of the onset of respiratory disease. Nevertheless, no date of onset was recorded for 17 of the patients, suggesting that data collection could be improved, especially as one of these patients was later reclassified as suspect. During the worldwide SARS epidemic in 2003, five case definitions were subsequently used in The Netherlands. The latest, used from 10 June onwards, was identical to that issued by the WHO on 1 May 2003. The three major criteria for SARS (i.e., respiratory disease, fever and travel-associated risk) were met in 25 (34%) cases. Of these, two patients had spent just a few hours in an airport in an affected area, and another two patients became ill outside the incubation period. Using the most sensitive case definition (WHO, 1 May 2003), 21 cases would have been considered as suspect, and two (2.8%) patients would have qualified as probable cases. These cases were not reported to the WHO because, at the time of their assessment, they did not meet the criteria for probable cases according to the prevailing Dutch case definition.

With strict application of the specific case definitions issued in The Netherlands (before adopting the WHO version on 10 June 2003), only nine cases would have been defined as suspect cases requiring SARS assessment. In reality, despite the case definitions used, 52 cases were

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considered to be suspect by the clinician or the local public health officer. In the UK, over 400 cases were referred for assessment, among which four probable cases were identified [21]. In France, 437 cases were notified, with seven being classified as probable cases, among which four were later confirmed as being infected with SARS-CoV [22].

The Netherlands was not a country affected by SARS, and there was no local transmission. SARS was ruled out on the basis of the criteria in force at that time. As soon as SARS-specific diagnostic tests became available, they were used on samples from 37 patients. Acute sera taken early in the course of the infection can result in false-negative serological results unless convalescent sera are also analysed at a later date. Negative serology was not the only criterion for ruling out SARS; discharge from observation took place only when the clinical course improved and/or an alternative diagnosis could fully explain the illness.

Although inevitable following the gradual accumulation of knowledge during the SARS outbreak, the changes in case definitions during the epidemic caused confusion in the management of individual cases. Subsequently, greater knowledge of the disease has revealed that transmission occurred mainly within hospitals caring for seriously-ill patients. The severity of the disease (pneumonia or respiratory distress syndrome) is an important criterion for including patients in the suspect group, and for referring them for further assessment in countries considered to be at low risk according to the WHO classification [23]. To increase the assessment specificity, the inclusion of significant travel exposure (i.e., contact with a person suffering from respiratory disease in areas with local transmission) or hospital exposure (i.e., the patient has been hospitalised or has been working in a risk area for SARS) should be obligatory when considering SARS in patients returning from abroad. Issartel *et al*. [24] concluded that contact exposure seemed to be one of the best criteria for identifying cases of suspected SARS.

A limitation of the present study is that, in the absence of confirmed SARS cases in The Netherlands, it is not possible to identify with certainty which components of the criteria for SARS assessment would be crucial in identifying genuine cases. In the early stages of SARS (or during a new incident), the vital diagnostic features will emerge only with time, and the criteria for separating cases from non-cases will initially be imprecise. Continuous vigilance by healthcare professionals and public services will provide the basis for identifying possible cases. From a public health point of view, in order to prevent the medical services from becoming overwhelmed, a first-line filter is needed to separate suspect cases from not-suspect cases before referring patients for further assessment. The first-line filter will be based on broad clinical and epidemiological criteria (e.g., history of contact and travel exposure) and will be refined gradually as knowledge concerning this disease becomes available.

Education of health professionals in the use of case definitions is needed before the event. Risk assessment and case classification should be done by individuals with experience in working with SARS case definitions. This could be achieved within a centralised surveillance and assessment system by an expert team with clinical and public health expertise (i.e., knowledge of the epidemiological features of the disease and the availability of necessary additional resources) [25]. This expert team, with both the necessary experience and the authority to confirm the suspicion, should be available at all times. Centralised assessment is appropriate as long as there are only imported cases, or local transmission remains at a low level. This approach might have limitations for countries in which a delay in isolating patients could occur because of large distances between hospitals. This is undesirable because shortening the period between the onset of symptoms and isolation, and proper management of contacts, have proven to be effective in containing SARS. The risk of secondary transmission has been shown to decrease significantly when cases are isolated within 3 days of the onset of symptoms [26,27]. Telephone or online consultation with the expert team is a useful option.

In the coming years, and particularly during the seasonal increase in respiratory disease in autumn, the burden of managing non-SARS cases will be high, and public anxiety should not be increased unnecessarily by the use of a case definition that is overly non-specific for a country at low risk. A possible disadvantage of using too narrow a case definition is that missed cases could prove to be super-spreaders. This risk will come from unrecognised cases; however, sub-clinical infections seldom occur, and significant virus

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shedding with secondary transmission has been documented mainly in the second week after the onset of disease [28,29].

Individual situations vary, and no single set of assessment criteria can be applied to all settings. Some of the dilemmas encountered with SARS will reappear when worldwide threats provided by pandemic influenza, (re)emerging pathogens or bioterrorism occur. Compared with other infectious diseases, SARS has an estimated low R_0 (basic reproduction number) [26], and transmission is confined mostly to spread from overt clinical cases. The extent of transmission of influenza by sub-clinical cases during a pandemic is difficult to predict, and in such a situation, timely preparedness and proper allocation of resources to manage both suspect cases and non-cases, and their contacts, are important. The danger of over-reporting cases should be taken into account when estimating and planning epidemic control resources before an outbreak occurs. The costs of managing non-cases should not be underestimated, as they require thorough assessment and the instigation of public health measures, thereby increasing existing workloads.

Both within the process of scientific advice and the preparation of outbreak plans, the consequences of the various case definitions should be considered, in addition to the training of professionals in applying case definitions to their patients. A first-line filter for separating non-cases from suspect cases should be followed by consultation with a centre of expertise, bearing in mind that the balance between the need to classify and manage cases correctly and the need to allay public anxiety quickly could be delicate.

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