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Autochthonous dengue virus infection in Japan imported into Germany, September 2013

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In September 2013, dengue virus (DENV) infection was diagnosed in a German traveller returning from Japan. DENV-specific IgM and IgG and DENV NS1 antigen were detected in the patient's blood, as were DENV serotype 2-specific antibodies. Public health authorities should be aware that autochthonous transmission of this emerging virus may occur in Japan. Our findings also highlight the importance of taking a full travel history, even from travellers not returning from tropical countries, to assess potential infection risks of patients.

Here we report the clinical and laboratory findings of a dengue virus (DENV) infection acquired in Japan in late summer 2013 and imported into Germany.

Case description

A previously healthy woman in her early 50s sought treatment in a hospital in Berlin, Germany, in September 2013 after returning from travel to Honshu Island, Japan. For the previous six days, she had been suffering from fever (up to 40 °C) and nausea, followed by a maculopapular rash. Laboratory tests on the day of admission showed elevated levels of glutamate-oxalate transaminase (GOT) (96 units (U)/L; norm: <35 U/L), glutamate pyruvate transaminase (GPT) (52 U/L; norm: <35 U/L), creatine kinase (CK) (553 U/L; norm: <170 U/L) and lactate dehydrogenase (LDH) (299 U/L; norm: <250 U/L). Leukopenia (white blood cell count: 3.2 G/L; norm: 4.4–11.3 G/L) was present, which intensified the following day (3.1 G/L). In addition, thrombocytopenia, with a platelet count of 87 G/L (norm: 177–393 G/L) was present, which intensified the following day as well (79 G/L).

Nine days before admission, she had returned from a two-week trip to Japan, during which she visited Ueda, Fuefuki, Hiroshima, Kyoto and Tokyo in August. She reported several mosquito bites while grape picking in Fuefuki. She flew nonstop from Frankfurt International Airport to Tokyo Narita International Airport and came back the same way. The patient was vaccinated against yellow fever in 2009, because she had travelled to Kenya that year. In the beginning of 2012, she travelled to Singapore. Among several other diseases, dengue fever was suspected, because of the clinical picture.

The first serum sample, collected seven days after symptom onset, gave a positive result in DENV IgM and IgG antibody tests (in-house indirect immunofluorescence assay (IIFA), according to [1-3]), as well as for DENV nonstructural protein-1 (NS1) antigen tested by ELISA (Bio-Rad Platelia Dengue NS1 Ag) and a rapid test (SD BIOLINE Dengue Duo NS1 Ag + Ab Combo), demonstrating an acute DENV infection (Table). Real-time RT-PCR for DENV RNA [4] and generic flavivirus RT-PCR [5] were negative.

The thrombocytopenia resolved without complications and after one week in hospital, the patient was discharged with a characterisation of restitutio ad integrum (restoration to original condition). A follow-up serum sample was collected in December 2013, 110 days after symptom onset, because this acute case of dengue fever imported from Japan was considered very unusual. This second serum sample revealed a significant decrease in DENV IgG titre in the IIFA and negative results for DENV NS1 antigen (ELISA and rapid test) and DENV IgM (IIFA and rapid test) (Table). In order to identify the causative DENV serotype, an immune complex binding ELISA [6] was performed on the second serum sample, demonstrating the presence of DENV serotype 2-specific antibodies (Table) and the absence of DENV serotype 1-, 3- and 4-specific antibodies, thus excluding a secondary DENV infection.

Background

DENV is an arthropod-borne RNA virus of the *Flaviviridae* family causing dengue fever in humans. *Aedes aegypti*

Table

Serological results of case of autochthonous dengue virus infection in Japan imported into Germany, September 2013

Antibody or antigen tested	Serum samples taken after symptom onset (days)	
	7	110
Anti-DENV-IgG[a]	1:20,480	1:640
Anti-DENV-IgM[a]	1:320	<1:20
DENV NS1[b]	Positive (5.1 arbitrary units)	Negative (0.2 arbitrary units)
DENV serotype[c]	Not tested	DENV 2
Anti-JEV-IgG[a]	1:20,480	1:640
Anti-JEV-IgM[a]	<1:20	<1:20
Anti-WNV-IgG[a]	1:5,120	1:1,280
Anti-WNV-IgM[a]	<1:20	<1:20
Anti-YFV-IgG[a]	1:5,120	1:640
Anti-YFV-IgM[a]	<1:20	<1:20
Anti-TBEV-IgG[a]	1:640	1:320
Anti-TBEV-IgM[a]	<1:20	<1:20

DENV: dengue virus; JEV: Japanese encephalitis virus; TBEV: tick-borne encephalitis virus; WNV: West Nile virus; YFV: yellow fever virus.

[a] Indirect immunofluorescence assay (IIFA) titres <1:20 for serum were considered negative [1-3].
[b] SD BIOLINE Dengue Duo NS1 Ag + Ab Combo and Bio-Rad Platelia Dengue NS1 Ag.
[c] Immune complex binding ELISA [6].

(Linnaeus) and *Ae. albopictus* (Skuse) mosquitoes are considered to be the main vectors of DENV worldwide [7]. DENV has emerged in recent decades as a worldwide public health problem: current estimations assume 390 million DENV infections per year, with 96 million clinically apparent cases [7]. The virus is found in tropical and subtropical regions around the world, with hyper-endemic areas in Central and South America and in south-east Asia. It is considered an emerging threat to Europe because of its detection in Croatia (2010) and France (2010 and 2013) [1,8,9]. *Ae. albopictus* is considered to be the potential vector for DENV in these countries: it is an invasive species in Europe and was recently detected in the south-western and south-eastern parts of Germany [10,11].

In Germany, dengue fever is notifiable and 870 imported cases were reported in 2013, with the majority of cases imported from south and south-east Asia [12]. There is no evidence for autochthonous transmission in Germany.

In Japan, *Ae. albopictus* is well established and distributed widely, with its northern limits on Honshu Island between latitude 38 ° to 40 ° north [13]. Moreover, *Ae. aegypti* is also invasive in Japan and was detected during entomological surveillance at Tokyo Narita

International Airport in 2012 [14]. The last notable dengue fever outbreak in Japan occurred in 1942 to 1945 in Nagasaki, Kyushu Island, and spread in 1944 to cities on Honshu Island such as Hiroshima and Osaka [15]. This was the most widespread dengue epidemic recorded in a temperate region, involving at least 200,000 cases [16]. It was suggested that the principal vector was *Ae. albopictus* [13]. However, no autochthonous cases of dengue infection have been reported since 1945 [16]. According to Japanese notification data, 249 imported DENV infections were reported in 2013 [17]. The reported DENV infections were mainly caused by DENV serotype 1 [17].

Conclusions

This is the first laboratory-confirmed case of DENV infection imported from Japan to Germany and, to the best of our knowledge, the first recognised case of locally acquired DENV infection in Japan for more than 60 years. Most likely, according to the patient's activities and DENV incubation period (3–14 days [18]), the infection was acquired in Fuefuki during grape picking. However, other possible places of infection cannot be entirely ruled out including Tokyo Narita International Airport. Thus, we suggest that a viraemic patient was bitten by a competent mosquito (most likely *Ae. albopictus*) in the geographical area where our patient was picking fruit, leading to the amplification of DENV serotype 2 in the local mosquito population. Such an event was probably the source of the virus that infected our patient.

This case adds important epidemiological data that can be used to refine DENV risk assessments in Japan. Consequently, the Ministry of Health, Labour and Welfare of Japan was informed via the International Health Regulations National Focal Point about the case. Public health authorities, blood transfusion services and clinicians in Japan should consider the risk of autochthonous DENV infections, especially during the summer. Our findings also highlight the importance of taking a full travel history, even from travellers who do not return from tropical countries, in order to assess potential infection risks of the patients [18].

Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: JSC, SG, DT, CF, KS, DS, IS; performed laboratory or epidemiological investigations: JSC, PE, KS, CF, DS, SS, DW, KH, DS; performed data analysis: JSC, PE, CF.

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A new laboratory-based surveillance system (Respiratory DataMart System) for influenza and other respiratory viruses in England: results and experience from 2009 to 2012

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During the 2009 influenza A(H1N1) pandemic, a new laboratory-based virological sentinel surveillance system, the Respiratory DataMart System (RDMS), was established in a network of 14 Health Protection Agency (now Public Health England (PHE)) and National Health Service (NHS) laboratories in England. Laboratory results (both positive and negative) were systematically collected from all routinely tested clinical respiratory samples for a range of respiratory viruses including influenza, respiratory syncytial virus (RSV), rhinovirus, parainfluenza virus, adenovirus and human metapneumovirus (hMPV). The RDMS also monitored the occurrence of antiviral resistance of influenza viruses. Data from the RDMS for the 2009–2012 period showed that the 2009 pandemic influenza virus caused three waves of activity with different intensities during the pandemic and post pandemic periods. Peaks in influenza A(H1N1)pdm09 positivity (defined as number of positive samples per total number of samples tested) were seen in summer and autumn in 2009, with slightly higher peak positivity observed in the first post-pandemic season in 2010/2011. The influenza A(H1N1)pdm09 virus strain almost completely disappeared in the second post-pandemic season in 2011/2012. The RDMS findings are consistent with other existing community-based virological and clinical surveillance systems. With a large sample size, this new system provides a robust supplementary mechanism, through the collection of routinely available laboratory data at minimum extra cost, to monitor influenza as well as other respiratory virus activity. A near real-time, daily reporting mechanism in the RDMS was established during the London 2012 Olympic and Paralympic Games. Furthermore, this system can be quickly adapted and used to monitor future influenza pandemics and other major outbreaks of respiratory infectious disease, including novel pathogens.

Introduction

The long-standing national laboratory surveillance system in England known as LabBase [1] collects positive reports of detections of a wide range of infectious pathogens, but does not collect negative results. Two sentinel general practitioner virological surveillance schemes, the Royal College of General Practitioners (RCGP) and Public Health England (PHE, the former Health Protection Agency (HPA) is part of PHE from April 2013) scheme (RCGP/PHE scheme) [2–5], and the PHE and Regional Microbiological Network (RMN) swabbing scheme (PHE/RMN scheme) [6], have been in operation in England since the early 1990s to monitor influenza activity in primary care settings (i.e. community settings) during the winter period. As part of strengthening respiratory virus surveillance in response to the 2009 influenza A(H1N1) pandemic [7–10], a new laboratory-based respiratory virus surveillance system, the Respiratory DataMart System (RDMS), was developed in England in 2009. This laboratory surveillance system was initially established to collect both positive and negative results for the specific detection and confirmation of infection with influenza A(H1N1)pdm09 virus from a network of laboratories in England using a newly implemented PCR assay [11] . The system was later extended to facilitate the monitoring not only of influenza virus but also of other major respiratory viruses, including respiratory syncytial virus (RSV), human metapneumovirus (hMPV), rhinovirus, parainfluenza viruses, and adenovirus. The primary objective of the RDMS as a new surveillance system is to alert relevant stakeholders on the incidence trends of these viruses. The RDMS operates all year round collecting results of

all routinely tested respiratory clinical samples from participating laboratories. These samples have been taken from both primary and secondary healthcare settings. This paper describes this new RDMS system and results from data collected during the pandemic and post-pandemic periods between 2009 and 2012. It also provides a preliminary evaluation of this new system in comparison with other existing surveillance systems.

Methods

A network of 14 laboratories representing all nine regions of England currently participates in the RDMS, including the national reference laboratory (the PHE Respiratory Virus Unit (PHE-RVU) of the Virus Reference Department, Colindale, London), all major PHE regional laboratories and four local National Health Service (NHS) laboratories. All participating laboratories, except the PHE-RVU, provide routine respiratory virus diagnostics service for their affiliated major regional or local hospitals.

Laboratory tests are requested by clinicians in charge of patient care. Clinicians decide the test each patient needs, and which types of samples need to be taken, and when. The most common sample types reported to this system are nasopharyngeal aspirate, tracheal secretion and nasal and throat swab. This system does not collect data on patients' clinical condition or case definitions used by clinicians.

All participating laboratories detect influenza, RSV, rhinovirus, parainfluenza 1–4 and hMPV using reverse transcription real-time polymerase chain reaction (rRT-PCR), and adenovirus using real-time PCR. All laboratories validated their assays appropriately. Quality assurance is achieved by participation in External Quality Assurance (EQA) programmes.

All respiratory virus test results are submitted to RDMS every week throughout the year. Both positive and negative results are submitted. The test results of influenza A(H1N1)pdm09 were collected and stored in another system before the establishment of the RDMS in November 2009. These results were transferred into the RDMS. Since November 2009, results for other respiratory viruses tested in routine respiratory virus PCR systems (including RSV, rhinovirus, parainfluenza 1–4, adenovirus and hMPV) have also been included in the RDMS.

Influenza A subtyping results were reported by 10 of the 14 participating laboratories; one laboratory carried out the test but results have not yet been reported, and the remaining three laboratories did not perform influenza subtyping.

As part of daily respiratory virus surveillance for the London 2012 Olympic and Paralympic Games, a subset of seven major participating laboratories undertook daily data submission from April to September 2012 to feed into the internal PHE's daily national Olympic situation reports produced during the Games period between July and September 2012.

Although participating laboratories employ different laboratory information management systems (such as Winpath, Telepath and Apex) and data codes, a standard common set of data items has been defined, including items such as sex, date of birth, sample date and virological test results for each virus. Programmes have been developed which standardise these data for combination in a central database. Data submission is carried out through a secure online data submission tool. De-duplication is carried out during data importation using a six-week episode period, which is consistent with the PHE national laboratory database, LabBase [1], and is intended to capture all possible test results relating to the same episode of a respiratory infection.

Submitted data contain all test results carried out by the 14 participating laboratories for all respiratory samples taken from hospital inpatients, hospital outpatients, and patients in primary care settings. Samples collected through both the RCGP/PHE and PHE/RMN sentinel general practitioners (GP) schemes from patients in the community are also included in the RDMS.

The proportion of samples positive (positivity) for viruses under surveillance is calculated (based on weekly samples tested) by virus type and by age group (<5, 5–4, 15–44, 45–64 and 65+ years) using weekly number of positive detections divided by the weekly total number of samples tested. Positivity was not calculated when the sample size was less than 10 in our study. A three-week moving average of the positivity is used to smooth the random fluctuation of the weekly positivity. The data are analysed to determine trends and predominant virus types. To compare the RDMS with other existing surveillance systems, the overall proportion of samples positive (positivity) for influenza during the 2010/11 and 2011/12 winter seasons are used with the results from other influenza surveillance systems including the weekly influenza-like illness (ILI) GP consultation rates (weekly number of ILI patients per 100,000 GP registered population) reported from the Research & Surveillance Centre of the Royal College of General Practices (RCGP) [5, 12–15]; the proportion of total weekly calls made through to the NHS Direct (NHSD) telephone helpline in England for fever in 5–14 years (NHSD Fever) [16–19], and the community influenza positivity using the combined overall proportion of samples positive for influenza (including all types/subtypes of influenza) from the two community-based GP sentinel virological surveillance schemes (the RCGP/PHE scheme [2–5] and the PHE/RMN scheme [6]). The original weekly data values for various indicators from other systems were available and examined in comparison with this new RDMS system for season start, peak time and trend.

Weekly number of samples submitted to Respiratory DataMart System during influenza and non-influenza seasons, England, April 2009–July 2012

Study period	Range of sample numbers per week during influenza season (week 40–week 20)	Range of sample numbers per week during non-influenza season (week 21–week 39)
Apr 2009–Sep 2009	NA	600–10,000[a]
Oct 2009–Sep 2010	400–4,000	300–500
Oct 2010–Sep 2011	500–6,000	200–500
Oct 2011–Jul 2012	500–1,000	200–500

NA: not applicable.

[a] First wave of the 2009 influenza pandemic.

A subset of four laboratories, including the PHE-RVU, also submit influenza antiviral susceptibility testing results for oseltamivir (from all these four laboratories) and zanamivir (from the PHE-RVU only). Three regional laboratories perform a real-time genotyping PCR for rapid discrimination of a single nucleotide change (tyrosine to histidine at position 275; H275Y mutation) in the neuraminidase gene of influenza A(H1N1)pdm09 viruses that confers oseltamivir (Tamiflu) resistance (methodology available on request). PHE-RVU confirm oseltamivir-resistant virus detections from the regional laboratories and perform additional screening of A(H1N1)pdm09 viruses for the H275Y mutation using pyrosequencing methodology as previously described [20]. In addition, PHE-RVU analyses virus isolates with sufficient neuraminidase activity phenotypically for susceptibility to oseltamivir and zanamivir, by a fluorescence-based neuraminidase enzyme inhibition assay, described previously [21].

A weekly report is produced, based on the RDMS data of influenza and other respiratory viruses, to track the weekly number of positive results and weekly proportion of positives (positivity) by sampling week, age group and virus type which is summarised in the PHE Weekly National Influenza Report [22] and in the accompanying graph collection on the PHE website [23].

The process of data collection, management and application for RDMS has been approved by the National Information Governance Board for Health and Social Care.

Results

The number of respiratory samples reported to RDMS from participating laboratories is summarised in Table 1.

The sample source data is currently only available from three participating laboratories, including the national reference laboratory (PHE-RVU) and two regional laboratories. This represents 43,949 of all 201,537 samples collected from all participating laboratories in the RDMS up to week 27 2012. The sample source data from two regional laboratories indicates that the biggest proportion of RDMS samples (68.3%) were from patients admitted into secondary care settings (mainly hospital inpatients), with 3.0% from primary care settings and the rest (28.7%) from other sources (unspecified or unnamed sources). However, the sample source data from PHE-RVU shows that the majority of samples (88.7%) were from primary care settings, with only 11.3% from secondary care settings. Information is not currently available on sample source from the remaining 11 laboratories.

The RDMS database was set up as a weekly reporting system, although seven laboratories reported daily data during the 2012 Olympic and Paralympic Games period. The reporting delay time from sampling date to the date of the results reported to the RDMS was examined and showed that 63.6% of sample results were reported to the system within a week of sampling, 95.8% within two weeks and 98.1% within three weeks.

Results for influenza by type and subtype are shown in Figures 1a (overall) and 1b (by age group) from the start of the 2009 pandemic in April 2009 to July 2012 (week 27 2012), including the two pandemic waves of the 2009 influenza pandemic. Figures 2a and 2b show the number of positive detections and proportion of samples positive for other respiratory viruses (data available from November 2009) by sampling week and by age group, respectively, to week 27 2012.

The first wave of the 2009 pandemic occurred between late April 2009 and August 2009, with the peak weekly influenza positivity at 35.1% in June 2009. The second pandemic wave occurred between August 2009 and February 2010 with the peak positivity at 34.2% in October 2009 (Figure 1a). During the 2010/11 season, there was a single peak of activity with overall influenza positivity reaching 38.4%, and a low level of influenza B co-circulating (Figure 1a). During the 2011/12 season, the predominant strain in circulation was influenza A(H3) at a low level, reaching a peak of 17.6% in week 9 2012, with very few sporadic influenza A(H1N1)pdm09 viruses and some influenza B viruses (Figure 1a). Figure 1b shows a different age distribution between 2009/10, 2010/11 and 2011/12 seasons. During the 2009/10 pandemic period, the age group with the highest positivity was children aged between

FIGURE 1

Number of positive tests and proportion of positive results for influenza by influenza subtype and week (A) and proportion of samples positive for influenza by age group and week (B) England, April 2009–July 2012*
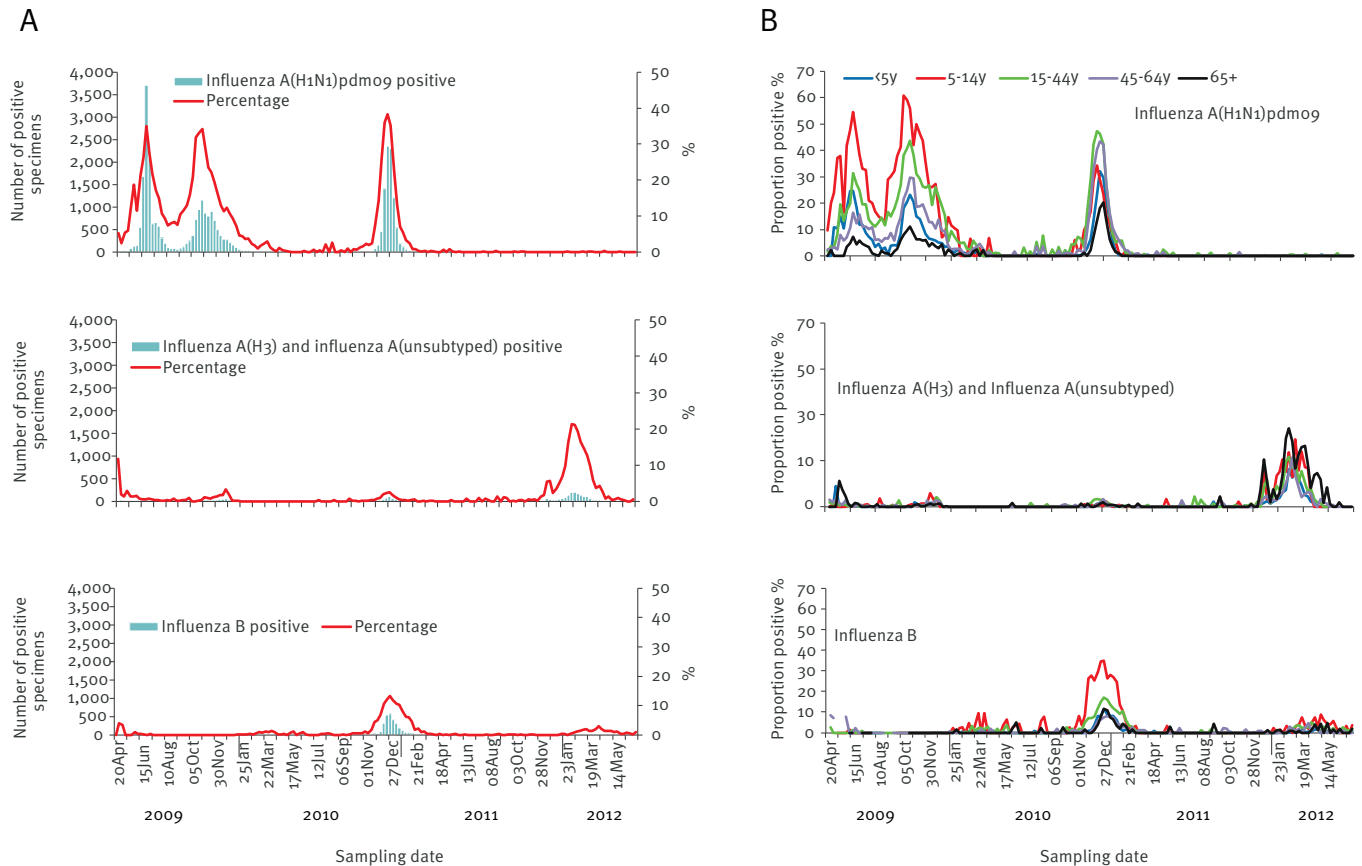
5 and 14 years old, followed by 15–44 year-olds. In the 2010/11 season, however, the age groups with highest positivity were 15–44 and 45–64 year-olds, for influenza A(H1N1)pdm09 infection. During the 2011/12 season, low levels of influenza A(H3) were similarly distributed between different age groups, with the over 65 year-olds having the highest peak in proportion positive. Influenza B circulation was mostly seen in the 5–14 year-olds during the 2010/11 season, with low circulation during the 2009/10 season and very low circulation during the 2011/12 season.

The weekly number of positive samples and three-week moving average of the weekly positivity for other respiratory viruses than influenza are shown in Figure 2a. Between November 2009 and July 2012, the proportion of respiratory samples positive for RSV peaked between November and December each year. The proportion positive for adenovirus does not demonstrate any obvious seasonal pattern. Parainfluenza virus detection (mainly parainfluenza type 3) peaked in April 2010 and April 2011, and in May 2012, although a lower second peak (mainly due to other parainfluenza types 1, 2 and 4) was seen in October 2011. Rhinovirus showed higher positivity for most of the year, with lower activity seen

during December 2009 and December 2010. Clear seasonality was also observed for hMPV with higher positivity between February and April, and lower positivity during summer and autumn.

The three-week moving averages of the weekly proportions of samples positive for other respiratory viruses by age group are shown in Figure 2b. Patients under 5 years of age usually had the highest proportion positive for all of these respiratory viruses. Patients aged 5–14 years also had a higher proportion positive for adenovirus and rhinovirus.

Results from the daily data submission had been extracted and used to produce the daily PHE national situation report (internal report) during the period of the 2012 Olympic and Paralympic Games. The numbers of positive detections of influenza by type and subtype and any significant findings from the daily data for other respiratory viruses were reported each day during the Games period.

In addition to the proportion positive results described above, the weekly proportion negative among these samples was also examined and shown in Figure 3.
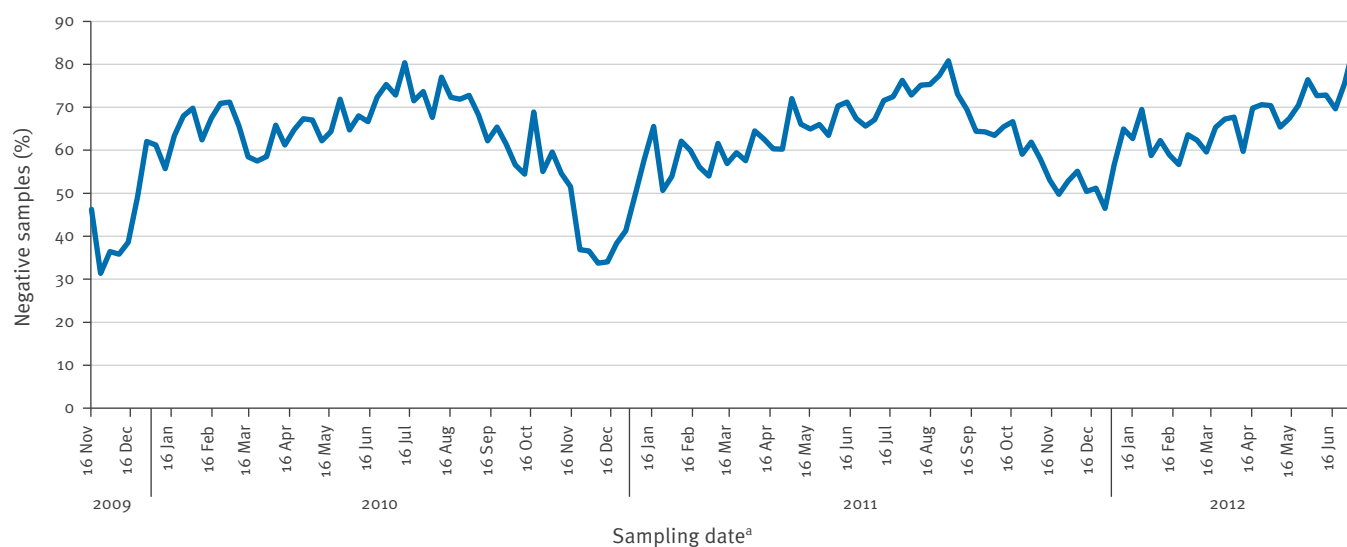
FIGURE 2

Number of positive tests per week and three-week moving average of proportion of positive results for major respiratory viruses other than influenza (A) and three-week moving average of the weekly proportion of samples positive for major respiratory viruses other than influenza by age group (B) England, November 2009 – July 2012*
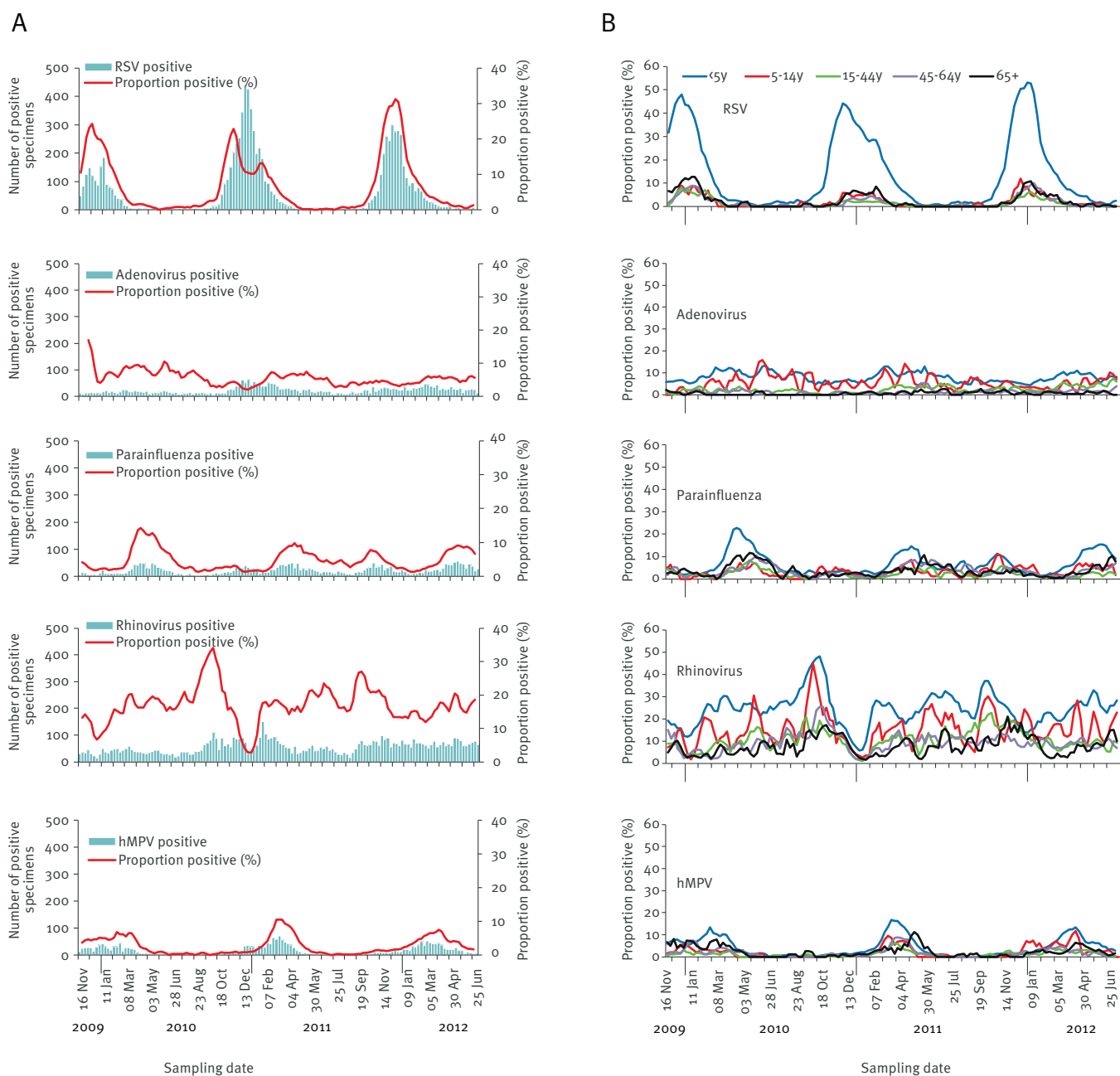
hMPV: human metapneumovirus; RSV: respiratory syncytial virus.

^a Samples were tested weekly.

This figure shows that during the study period, the proportion of samples testing negative for any intended respiratory viruses included in the RDMS system, i.e. influenza A and B, RSV, adenovirus, rhinovirus, parainfluenza and hMPV, demonstrated a clear seasonality with low proportion negative observed during the winter period and high proportion negative during the summer and autumn period.

A comparison of the results of RDMS with other existing influenza activity surveillance systems in England is shown in Figure 4. The RDMS weekly influenza proportion positivity was lower but demonstrated a steady trend compared with the community influenza positivity (Figure 4). The first signals of the start of the 2010/11 season's influenza activity were seen from the NHSD fever calls in the 5–14 year-olds which started to increase from week 45 2010 and rose above the season's threshold level of 9% from week 47 2010, together with the community influenza positivity and RDMS influenza positivity which started to increase significantly from week 47 2010 and peaked between weeks 50–52 2010. The RCGP consultation rates increased significantly from week 49 2010 and peaked in week 51 2010, with a second peak in week 1 2011 (which may be due to delayed consultation over the Christmas and New Year holiday). The 2011/12 season's influenza activity was low and came late, increasing slowly from week 3 2012, with the first increase observed from the RDMS influenza positivity in week 2 2012 followed by the community influenza positivity one week later. Positivity peaked during weeks 7 2012 and 8 2012.

Table 2 shows the antiviral test results reported to RDMS by four participating laboratories performing antiviral susceptibility testing, including PHE-RVU, during the 2010/11 and 2011/12 seasons. Three regional laboratories reported oseltamivir susceptibility testing data, accounting for 25.7% of all tests (screening for the H275Y mutation in the neuraminidase gene of influenza A(H1N1)pdm09 viruses), although the majority of antiviral susceptibility test results for influenza A and all test results for influenza B came from the PHE-RVU which carries out UK-wide confirmatory testing for any oseltamivir resistance detections and all zanamivir resistance tests. A total of 59 (3.3%) oseltamivir-resistant influenza A(H1N1)pdm09 viruses were detected during the 2010/11 season in the UK. No oseltamivir -or zanamivir-resistant influenza virus was detected up to week 27 2012 for the 2011/12 season. In addition, 63 of the influenza A(H3) viruses detected during the 2011/12 season have also been tested against M2 inhibitors (amantadine and rimantadine) by the PHE-RVU. All are resistant, with the S31N substitution, which is as expected for the circulating strain during that period.

Discussion

This article presents the findings of a new laboratory-based respiratory virus surveillance system, the Respiratory DataMart System (RDMS), which was developed and implemented during the influenza A(H1N1) 2009 pandemic in England. The system provides useful information in a timely fashion which has contributed to describing the epidemiology of influenza and other respiratory viruses during the 2009 pandemic and the two post-pandemic influenza seasons (2010/11 and 2011/12). The system is also able to monitor a range

Comparisons between Respiratory DataMart System and other monitoring systems for respiratory viruses by week, England, 2010/11 and 2011/12
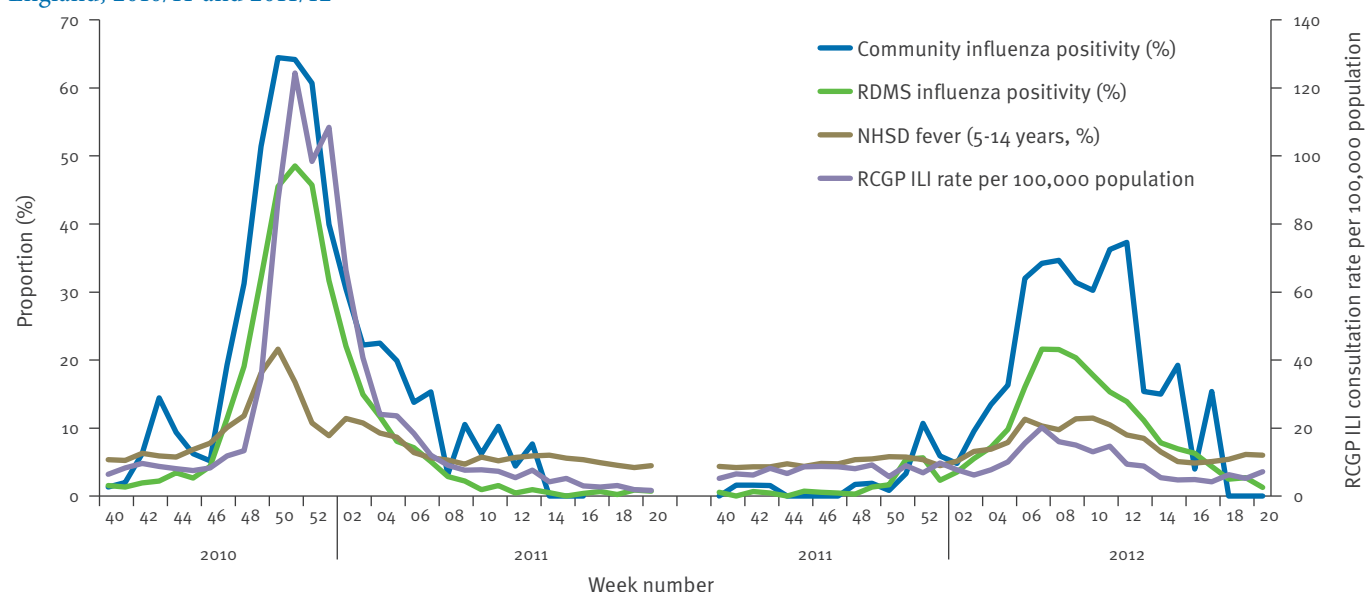
ILI: influenza-like illness; NHSD: NHS Direct; RCGP: Centre of the Royal College of General Practices; RMDS: Respiratory DataMart System.

of other respiratory viruses and influenza antiviral susceptibility. Comparison of this new system (RDMS) with other established surveillance systems shows that it consistently enables us to detect the start of the influenza season at an early time. The system was also successfully used for near real-time, daily surveillance during the London 2012 Olympic and Paralympic Games.

Data from the RDMS system show that the 2009 pandemic virus in 2009/10 had two waves, followed by a further post-pandemic wave in 2010/11, with the most affected age group shifting from 5–14 years in 2009/10 to 15–44 years in 2010/11. In the 2011/12 season which followed, the 2009 pandemic virus circulated very little, with low levels of influenza A(H3) as the predominant strain. This phenomenon has been observed elsewhere in Europe [24] and very low levels of the influenza A(H1N1)pdm09 strain were reported in the northern hemisphere except for Mexico, where it was the predominant strain. Overall levels were low in the United States and Canada during the 2011/12 season [25]. The RDMS system was also able to provide the data to the level of influenza subtype, which is critical in order to understand the epidemiology of influenza each season.

It may also be possible to use RDMS to describe the epidemiology of a range of other respiratory viruses. RSV was the most notable of these, with a high number of positive samples detected and high positivity. The marked regular seasonality of RSV activity was clearly displayed over the study period, peaking each November/December, with the most affected

population being children aged under five years. These features of seasonality and the different impact on various age groups have previously been recognised [26-28]. Clear seasonality was also found for parainfluenza viruses peaking in April to May and hMPV in February to April each year. Children under the age of five years were predominantly affected by both viruses. These findings were also consistent with previous studies [27–31]. No clear seasonality was found for adenovirus and rhinovirus, with rhinovirus being the second most reported virus in the RDMS following RSV and mainly affecting children under five years old.

Surveillance for influenza is common practice in most European countries [32] but routine surveillance for other respiratory viruses is not common. The RDMS thus provides a new mechanism to monitor the epidemiology of acute respiratory viral infections in a timely fashion.

The number of laboratories that submit data varies by week, which will have an impact on the number of samples received, an issue also seen with LabBase. Therefore, the absolute number of positive detections each week may not be a reliable indicator for disease surveillance purposes. The proportion of samples positive, however, can be a useful additional indicator in situations where the sample size is large enough. There was a drop in the proportion of tests positive in early June 2009 for influenza A(H1N1)pdm09 which occurred (Figures 1a and 1b) a few weeks before the first peak in number of cases in late June 2009. This was due to a significantly increased number of samples being tested in that week, especially in the 5–14

Laboratory	Influenza type / subtype	Oseltamivir						Zanamivir					
		Resistant		Sensitive		% Resistant		Resistant		Sensitive		% Resistant	
		2010/11	2011/12	2010/11	2011/12	2010/11	2011/12	2010/11	2011/12	2010/11	2011/12	2010/11	2011/12
HPA-RVU (UK-wide)	A(H3N2)	0	0	4	190	0	0	0	0	4	190	0	0
	A(H1N1) pdm09	59	0	1,382	5	4.1	0	0	0	155	1	0	0
	B	0	0	317	10	0	0	0	0	317	10	0	0
Manchester	A(H1N1) pdm09	1[a]	0	380	1	0.3	0	NT	NT	NT	NT	NT	NT
Birmingham	A(H1N1) pdm09	1[a]	0	40	0	2.4	NA	NT	NT	NT	NT	NT	NT
Southampton	A(H1N1) pdm09	1[a]	0	46	2	2.1	0	NT	NT	NT	NT	NT	NT
Total[b] (UK-wide)	A(H3N2)	0	0	4	190	0	0	0	0	4	190	0	0
	A(H1N1) pdm09	59	0	1,812	8	3.2	0	0	0	155	1	0	0
	B	0	0	317	10	0	0	0	0	317	10	0	0

HPA - RVU: Health Protection Agency – Respiratory Virus Unit; NA: not applicable; NT: not tested; UK: United Kingdom.

[a] This sample is also included in the HPA-RVU total.

[b] The figures in the total rows are figures after de-duplication.

year age group, while the number of positive samples only increased slightly over the same time period. This increased testing probably reflected the intensive pandemic case finding practice applied for early detection of suspected cases during the containment phase in the early stage of the 2009 pandemic in England [33] and highlights the value of the proportion positive indicator.

RDMS relies on patients being sufficiently unwell to seek medical care and being considered clinically suitable for testing. A number of other viral and bacterial respiratory pathogens are currently either not included in the test screen or not reported to the RDMS (e.g. *Mycoplasma pneumoniae*). Inclusion of these would affect the overall positivity of pathogen detection. Thus if numbers tested increased significantly but the proportion positive fell, this might reflect poor case finding but could also reflect an alternative respiratory pathogen being responsible for the presumed infection. The seasonality shown in the analyses of the proportion negative may indicate some contribution from other pathogens not included in the RDMS database, although this seasonality may be due mainly to the seasonal variations of respiratory viruses already included in the RDMS.

Daily surveillance data is in high demand, especially during events with high public health importance such as the London 2012 Olympic and Paralympic Games, and influenza pandemic or epidemic periods. It is a

great advantage for RDMS to be able to provide daily laboratory data to monitor influenza and other respiratory viruses. This daily surveillance operation can pick up early signs of increased activity of these viruses covered by the system and thus the ability to undertake prompt response and appropriate actions.

Comparing this new system (RDMS) with other established surveillance systems during the 2010/11 and 2011/12 influenza seasons shows that although the peak positivity values from RDMS are lower than from the community-based GP sentinel virological system (probably due in part to a much larger sample size in the RDMS), RDMS generally provides an early indication of the start of the influenza season. Figure 3 demonstrates that the RDMS data could act as an additional important source using routinely available laboratory data to detect the beginning of increased activity of influenza (and other respiratory viruses), and to track their epidemic trends.

The main strengths of the RDMS are that it collects both positive and negative test results all year round for influenza and several other common respiratory viruses. It is geographically representative: participating laboratories include all major regional laboratories plus several local laboratories across the country, with large sample numbers from both community and hospital settings. Similar positive numbers of influenza virus are reported to the RDMS and to the national LabBase database, which collects results from about

100 laboratories across the country, which indicates the completeness of reporting to the RDMS.

There are some limitations for this study. The lack of information on the source of the sample (i.e. primary vs secondary care settings) from many of the participating laboratories is one of them. However, the two regional laboratories where sample source data were available are very similar in terms of sample referral and test procedures, compared with the remaining 11 regional and local NHS laboratories. We therefore believe that the sample source results from these two regional laboratories should be generalisable, i.e. the majority of the samples for the regional and local NHS laboratories are from secondary care settings. Efforts are continuing to capture sample source information from the remaining laboratories.

This study covers the RDMS operation period for three influenza seasons between 2009 and 2012, during which time only the 2011/12 season was dominated by influenza A(H3). Therefore, longer period data from this system will be needed to further evaluate this system's ability to monitor the usual influenza A(H3) circulating situations, compared with other surveillance systems.

Virological surveillance of influenza and other respiratory viruses is crucial in order to determine which viruses are actually circulating in a population, and their timing, trend and impact. Using routinely available hospital laboratory data at minimum extra cost is an important addition to the current respiratory virus surveillance system. This approach has been tried in the US, which showed a good correlation with other influenza surveillance data during the 2009/10 pandemic period [34]. Hospital laboratory test results have been fed into some weekly influenza surveillance reports in some other European countries such as France and Denmark [35]. The RDMS has representative coverage of England, captures high volumes of samples and provides timely reports and feedback to data providers and stakeholders. It provides an important supplement to the routine influenza surveillance systems for both pandemic and seasonal influenza. With the accumulation of further years of data, thresholds and exceedance reports for each virus will become established. Furthermore, the RDMS can be easily adapted to add emerging pathogens, such as the novel coronavirus (MERS-CoV) or a new influenza pandemic virus.

Acknowledgments

*Erratum:

Figures 1 and 2 were erroneously swapped. This was corrected on 19 May 2014.

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