Prospective Evaluation of a New Automated Nucleic Acid Extraction System Using Routine Clinical Respiratory Specimens

C. Mengelle, J.-M. Mansuy, K. Sandres-Saune, C. Barthe, J. Boineau, and J. Izopet

The aim of the study was to evaluate the MagNA Pure 96™ nucleic acid extraction system using clinical respiratory specimens for identifying viruses by qualitative real-time PCR assays. Three extraction methods were tested, that is, the MagNA Pure LC™, the COBAS AmpliPrep™, and the MagNA Pure 96™ with 10-fold dilutions of an influenza A(H1N1)pdm09 sample. Two hundred thirty-nine respiratory specimens, 35 throat swabs, 164 nasopharyngeal specimens, and 40 broncho-alveolar fluids, were extracted with the MagNA Pure 96™ and the COBAS AmpliPrep™ instruments. Forty COBAS AmpliPrep™ positive samples were also tested. Real-time PCRs were used to identify influenza A and influenza A(H1N1)pdm09, rhinovirus, enterovirus, adenovirus, varicella zoster virus, cytomegalovirus, and herpes simplex virus. Similar results were obtained on RNA extracted from dilutions of influenza A(H1N1)pdm09 with the three systems: the MagNA Pure LC™, the COBAS AmpliPrep™, and the MagNA Pure 96™. Data from clinical respiratory specimens extracted with the MagNA Pure 96™ and COBAS AmpliPrep™ instruments were in 98.5% agreement (P < 0.0001) for influenza A and influenza A(H1N1)pdm09. Data for rhinovirus were in 97.3% agreement (P < 0.0001) and in 96.8% agreement for enterovirus. They were in 100% agreement for adenovirus. Data for cytomegalovirus and HSV1-2 were in 95.2% agreement (P < 0.0001). The MagNA Pure 96™ instrument is easy-to-use, reliable, and has a high throughput for extracting total nucleic acid from respiratory specimens. These extracts are suitable for molecular diagnosis with any type of real-time PCR assay.

BACKGROUND

The recent emergence of a new strain of influenza, influenza A(H1N1)pdm09, has emphasized the need for a rapid, high throughput system for identifying viruses in respiratory specimens. The diagnosis must also be able to differentiate between influenza A(H1N1)pdm09 itself and other respiratory viruses that may appear as complications. An influenza A(H1N1)pdm09 infection might lead to hospitalization in an intensive care unit where the number of available beds is limited [Fuhrman et al., 2011]. Molecular diagnosis of viral infections has become the “gold standard” in hospital laboratories and has replaced increasingly cellular virus culture and direct immunoassays. While real-time PCRs have improved biological management, the nucleic acid extraction step remains time-consuming and fully automated extraction instruments are needed. High quality real-time PCR assays to identify a broad range of viruses can only be performed on a high quality total nucleic acid extract.

The first automated systems able to extract nucleic acids from various clinical specimens had a limited capacity, no more than 24 or 32 samples. Several high throughput automated platforms are now available. They include the COBAS AmpliPrep™ (Roche Diagnostics, Meylan, France) [Sandres-Saune et al., 2007; Schumacher et al., 2007; Sizmann et al., 2007; Alp and Hascelik, 2009], the NucliSENS easyMAG

Abbreviations: IQC, intra-laboratory quality control; FRET, Fluorescence Resonance Energy Transfert; PCR Cp, PCR crossing point.

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(bioMérieux, Boxtel, The Netherlands) [Loens et al., 2007; Perandin et al., 2009; Pillet et al., 2009], the QIAGEN QIAsymphony SP (Qiagen, Valencia, CA) [Miller et al., 2010], and the m2000 system (Abbott Laboratories, North Chicago, IL) [Scott et al., 2009]. All of these systems are capable of extracting high quality virus nucleic acid, but they are still time-consuming and require 2–4 hr to extract 96 samples. The recently available MagNA Pure 96™ (Roche Diagnostics) claims to be able to extract nucleic acids from 96 samples in less than 1 hr.

**OBJECTIVES**

The aim of this study was to examine the performance of the MagNA Pure 96™ system and its convenience for routine use in comparison to the COBAS Ampliprep™.

The first test samples were a series of 10-fold dilutions of influenza A(H1N1)pdm09. They were all extracted using the MagNA Pure LC™, the COBAS Ampliprep™, and the MagNA Pure 96™ instruments (Roche). A series of clinical respiratory specimens were then analyzed using the MagNA Pure 96™ and the COBAS Ampliprep™ instruments by real-time PCRs.

**MATERIALS AND METHODS**

**Materials**

*Dilutions of a control specimen.* The influenza A(H1N1)pdm09 intralaboratory quality control (IQC) was diluted in minimum essential medium to obtain five 10-fold dilutions. This IQC was prepared from infected culture of Madin and Darby canine kidney cells with a clinical respiratory specimen.

The nucleic acids were extracted from each dilution in duplicate using three extraction systems: the MagNA Pure LC™, the COBAS Ampliprep™, and the MagNA Pure 96™

**Routine clinical specimens.** A total of 239 clinical respiratory samples were collected prospectively during 1 week between January 27, 2010 and February 4, 2010 by the Department of Virology, CHU Toulouse, France. The nucleic acids were extracted from these samples using the COBAS Ampliprep™ and the MagNA Pure 96™ instruments.

They were 35 throat samples collected on virologically adapted Viocult® (Kitvia, Labarthe Inard, France), 164 nasopharyngeal swab samples collected on Viocult®, and 40 broncho-alveolar fluids collected in sterile tubes.

Samples were tested for several viruses, including influenza A, influenza A(H1N1)pdm09, rhinovirus, enterovirus, adenovirus, varicella zoster virus, cytomegalovirus, and herpes simplex type 1 (Table I).

**COBAS Ampliprep™ selected positive samples.** Respiratory clinical samples tested positive for adenovirus (N = 15), cytomegalovirus (N = 9), enterovirus (N = 9), and HSV (N = 7) were also tested. They were nasopharyngeal specimens (adenovirus

| Virus | Type of specimens | PCR chemistry | Molecular test | Real-time instrument | Refs. |
|-------|-------------------|---------------|----------------|---------------------|-------|
| Influenza A | Throat sample | RealTime ready | Inf A/H1N1 Detection Set | Light Cycler 480 | 1 |
| Influenza A(H1N1)pdm09 | Nasopharyngeal sample | Sybr Green + melting curve | Home-brew | Light Cycler 2.0 | 2 |
| Rhinovirus | Nasopharyngeal sample | Hydrolysis probe | Home-brew | Light Cycler 2.0 | 3 |
| Enterovirus | Nasopharyngeal sample | Hydrolysis probe | Home-brew | Light Cycler 2.0 | 4 |
| Adenovirus | Nasopharyngeal sample | Hydrolysis probe | Home-brew | Light Cycler 2.0 | 5 |
| Varicella zoster virus | Bronchoalveolar fluid | FRET | Home-brew | Light Cycler 2.0 | 6 |
| Cytomegalovirus | Bronchoalveolar fluid | Hydrolysis probe | Home-brew | Light Cycler 2.0 | 7 |
| Herpes simplex virus 1 and 2 | Throat sample | FRET + melting curve | Home-brew | Light Cycler 2.0 | 8 |

FRET, Fluorescence Resonance Energy Transfer.
and enterovirus) and bronchoalveolar fluids (cytomegalovirus and HSV).

**Extraction**

Three systems were used: the MagNA Pure LC Total Nucleic Kit (Roche) on the MagNA Pure LC instrument, the COBAS Ampliprep Total Nucleic Acid Isolation kit (TNAI; Roche) on the COBAS Ampliprep instrument [Mengelle et al., 2008], and the MagNA Pure 96 DNA and Viral NA Small Volume Kit (Roche) on the MagNA Pure 96.

Input and output volumes were 200 and 100 µl on the MagNA Pure systems. The volumes were 500 and 75 µl on the COBAS Ampliprep.

**Molecular Amplification Tests**

PCR tests used are described in Table I. Influenza A and influenza A/H1N1pdm09 viruses were detected with the RealTime ready Inf A/H1N1 Detection Set with the RNA virus master according to manufacturer’s instructions on the Light Cycler 480 system (Roche Diagnostics). The set contained specific primer/probe mixes for detecting influenza A matrix protein 2 (M2) and the Mexico variant specific hemagglutinin HA1 (H1) in a single pass.

Rhinovirus was detected on the Light Cycler 2.0 real-time instrument with an in-house technique [Kares et al., 2004]. Samples underwent one step RT-PCR using the SYBR Green technique, and then melting curve analysis was used to identify rhinovirus.

Enterovirus [Verstrepen et al., 2002], adenovirus [Heim et al., 2003], varicella zoster virus [Espy et al., 2000], and cytomegalovirus [Mengelle et al., 2003] were detected on the Light Cycler 2.0 using in-house real-time PCRs.

Herpes simplex types 1 and 2 were detected on the Light Cycler 1.0 as previously described [Mengelle et al., 2004]. FRET technology was used on the melting curve analysis to differentiate between HSV-1 and HSV-2.

**Statistical Analysis**

Data were analyzed using Stata software 9.2 (StataCorp, College Station, TX). The Kappa Cohen test was used to compare the performances of the assays. A P-value of < 0.05 was considered significant.

**RESULTS**

**Analytical Performances Using a Control Specimen**

The five 10-fold dilutions of the IQC influenza A/H1N1/pdm09 were extracted each twice with the three extraction instruments, the MagNA Pure LC, the COBAS Ampliprep, and the MagNA Pure 96. Each extract was tested for influenza A (target M2) and influenza A/H1N1/pdm09 (target H1).

Influenza A and influenza A/H1N1/pdm09 viruses were detected in RNA extracted with all the three instruments from the undiluted IQC and in the 10⁻¹, 10⁻², and 10⁻³ dilutions.

Both targets were detected in both 10⁻⁴ dilutions extracted with the MagNA Pure LC and the MagNA Pure 96. Each extract was tested for influenza A (target M2) and influenza A/H1N1/pdm09 (target H1).

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**TABLE II. Detection of Influenza A (Target M2) and Influenza AH1N1(2009) (Target H1) on Extracts of 10-Fold Dilutions of an Influenza AH1N1(2009) Virus Culture With the MagNA Pure LC, the COBAS Ampliprep, and the MagNA Pure 96 Systems**

| Influenza AH1N1(2009) Detection Set | MagNA Pure LC | COBAS Ampliprep | MagNA Pure 96 |
|-----------------------------------|--------------|----------------|--------------|
|                                   | M2 target    | H1 target      | M2 target    | H1 target      | M2 target    | H1 target      |
|                                   | PCR Cp       | PCR Cp         | PCR Cp       | PCR Cp         | PCR Cp       | PCR Cp         |
| Pure                              | 21.98        | 21.4           | 27.47        | 24.13          | 24.29        | 22.35          |
| Pure                              | 21.92        | 21.11          | 26.63        | 24             | 24.5         | 22.55          |
| 10⁻¹                              | 25.24        | 24.4           | 30.48        | 27.85          | 27.28        | 25.39          |
| 10⁻²                              | 25.33        | 24.36          | 30.37        | 27.91          | 27.22        | 25.49          |
| 10⁻⁻²                             | 28.65        | 27.95          | 34.49        | 30.88          | 31.53        | 29.62          |
| 10⁻⁻²                             | 28.34        | 26.80          | 33.55        | 30.49          | 31.89        | 29.37          |
| 10⁻⁻⁻                             | 32.43        | 31.37          | 36.89        | 33.71          | 35.58        | 33.33          |
| 10⁻⁻⁻                             | 31.55        | 30.99          | 35.63        | 34.63          | 35.51        | 33.86          |
| 10⁻⁻⁻                             | 36.27        | 34.52          | 35.40        | Negative       | 39.07        | 36.34          |
| 10⁻⁻⁻                             | 33.71        | 34.73          | Negative     | 39.64          | 40.34        | 37.49          |
| 10⁻⁻⁻                             | Negative     | Negative       | Negative     | Negative       | Negative     | Negative       |

PCR Cp, PCR crossing point.

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Analytical Performances Using Routine Clinical Samples

Two hundred thirty-nine clinical respiratory samples were extracted prospectively with the COBAS Ampliprep™ and the MagNA Pure 96™ instruments. As the number of positive samples was too small, 40 additional COBAS Ampliprep™ positive samples were extracted with the MagNA Pure 96™ instrument. Prospective samples and retrospective positive samples were pooled for analysis.

Detection of RNA viruses. Sixty-four samples were tested for influenza A and influenza A(H1N1)pdm09. Three samples were influenza A (M2) positive, whereas 60 were negative. One nasopharyngeal sample was M2 positive with the MagNA Pure 96™ and M2 negative with the COBAS Ampliprep™. Two samples were influenza A(H1N1)pdm09 positive, and 61 were negative by both extraction methods. One sample was MagNA Pure 96™ negative and COBAS Ampliprep™ positive. The detections of influenza A and influenza A(H1N1)pdm09 were in 98.5% concordance ($P < 0.0001$).

Seventy-four samples were tested for rhinovirus: 16 samples were positive and 56 negative with both extraction systems. Two samples were MagNA Pure 96™ positive and COBAS Ampliprep™ negative. The detections were in 97.3% concordance ($P < 0.0001$). The results for enterovirus agreed 96.8%: 10 samples were positive and 20 were negative. Both techniques disagreed on one sample which was MagNA Pure 96™ negative (Table III).

Detection of DNA viruses. The two extraction systems agreed 100% for adenovirus: 15 samples were positive and 26 samples were negative, and for varicella zoster virus: six negative samples.

Twenty-one broncho-alveolar samples were tested for cytomegalovirus: 10 were negative and 10 were positive by both methods. One sample was MagNA Pure 96™ positive and COBAS Ampliprep™ negative. There was thus 95.2% concordance ($P < 0.0001$).

Detection of HSV1-2 gave 95.2% concordant results: 40 samples gave identical results, 10 samples were positive, and 30 were negative ($P < 0.0001$). The 10 positive results gave identical herpes virus types (HSV-1). One sample was MagNA Pure 96™ positive/COBAS Ampliprep™ negative and one sample gave the opposite result. Both samples were broncho-alveolar specimens containing very little herpes simplex type 1 (Table IV).

Practicality. The MagNA pure 96™ and the COBAS Ampliprep™ use the same technology: lysis to release nucleic acids that are then bound to the silica surface of added magnetic particles due to the chaotropic salt conditions and the high ionic strength of the lysing reagent.

The reagents supplied with both instruments are ready-to-use and may be kept at room temperature for about 30 days. However, the instruments are used very differently: samples are dispensed in steps of 24 samples onto the

### Table III. Detection of RNA Viruses

|                  | COBAS Ampliprep™ | MagNA Pure 96™ |
|------------------|------------------|----------------|
|                  | RealTime ready Inf A/H1N1 Detection Set |                  |
|                  | Target M         | Target H1      |
| Positive         | Negative         | Total          |
| Positive         | 3                | 1             | 4      |
| Negative         | 0                | 60            | 60     |
| Total            | 3                | 61            | 64     |
| Positive         | 2                | 1             | 3      |
| Negative         | 0                | 61            | 61     |
| Total            | 2                | 62            | 64     |
| Positive         | 16               | 2             | 18     |
| Negative         | 0                | 56            | 56     |
| Total            | 16               | 58            | 74     |
| Positive         | 10               | 0             | 10     |
| Negative         | 1                | 20            | 21     |
| Total            | 11               | 21            | 32     |

* Sample negative for H1.

* Sample positive for M2 with both extraction systems.

### Table IV. Detection of DNA Viruses

|                  | COBAS Ampliprep™ | MagNA Pure 96™ |
|------------------|------------------|----------------|
|                  | Adenovirus       | Zoster virus   | Cytomegalovirus | Herpes simplex virus |
| Positive         | Negative         | Total          | Positive         | Negative         | Total          |
| Positive         | 15               | 0             | 0               | 10               | 1             | 11             |
| Negative         | 0                | 26            | 26              | 0                | 10            | 10             |
| Total            | 15               | 26            | 41              | 10               | 11            | 21             |

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COBAS Ampliprep™, so that extraction of 96 samples takes at least 4 hr. The MagNA Pure 96™ instrument uses a 96-nozzle pipette head and 8–96 samples can be processed in a single run of less than 1 hr. The MagNA pure 96™ also requires an input volume of 200 μl, and elution provides 100 μl. Most real-time PCR tests require an input volume of 5–10 μl, so at least seven viruses can be detected in a single extract.

**DISCUSSION**

The performance of a new commercially available high throughput extraction system was evaluated and was compared with other, older systems on a standard sample and on routine clinical samples.

Similar results were obtained when RNA was extracted from dilutions of influenza A(H1N1)pdm09 with three systems, the MagNA Pure LC™, the COBAS Ampliprep™, and the MagNA Pure 96™. Previous studies on the quantification of EBV [Mengelle et al., 2008] and CMV [Mengelle et al., 2011] in whole blood found a good correlation between the MagNA Pure LC™ system and the COBAS Ampliprep™. Thus, these data show the importance of comparing the new extraction system, the MagNA Pure 96™, with another highly automatic instrument that uses identical technology, the COBAS Ampliprep™. For this purpose, total virus nucleic acid (DNA and RNA) was extracted from respiratory specimens with both instruments and then tested for several viruses (influenza A and influenza A(H1N1)pdm09, rhinovirus, enterovirus, adenovirus, varicella zoster virus, cytomegalovirus, and herpes virus types 1 and 2) by real-time PCRs.

Previous studies have shown that high throughput automated extraction systems can be used for nasopharyngeal aspirates [Chan et al., 2008], plasma [Miller et al., 2010], and EDTA whole blood samples [Pillet et al., 2009]. Chan et al. compared two automatic extraction systems (the NucliSENS easyMAG and the Qiagen BioRobot 9604) with the manual QIAamp (Qiagen) extraction method. They found no difference in the sensitivities of all three methods. Furthermore, until recently the MagNA Pure LC™ system has provided an easy-to-use platform for extracting various clinical specimens. But we believe this is the first report of using the MagnA Pure 96™ instrument to extract nucleic acids from a large number of routine clinical respiratory specimens, including broncho-alveolar fluids, throat samples, and nasopharyngeal samples that were collected in 1 week during the influenza A(H1N1)pdm09 pandemic. The results show that the two extraction systems performed very similarly on all the clinical respiratory specimens regardless the real-time PCR technology used. Moreover, the methods performed similarly regardless of the structure of the viruses (DNA and RNA, with or without an envelope). The viruses tested can serve as models for all other viruses, including influenza B, respiratory syncytial virus, and coronaviruses. Some of these viruses, such as varicella zoster virus, are rarely found in respiratory infections, but as this was a prospective study, all the items requested by the clinicians were tested.

The use of this new automated system entails no change in sample preparation. Samples are diluted and mixed in minimum essential medium before extraction, and no extra medium, such as N-acetyl cysteine, is necessary.

The MagNA Pure 96™ can extract 96 samples in less than 1 hr and several extractions can be run in a single day if necessary. The advent of the MagNA Pure 96™ has lead to huge changes in the organization of the laboratory. Two extractions a day are now run, so clearing all daily incoming clinical specimens. In addition, as elution volume is 100 μl, only a single extraction is needed even if several PCR tests are to be done. This greatly reduces the technician's hands-on time and hence the cost of the entire PCR test. As most PCR assays are now carried out on the same day, the waiting time for results has decreased dramatically, as have the number of phone calls from clinicians.

The MagNA Pure 96™ software is easy-to-use, so that technicians do not require a long initial training. Maintenance is also easy; it requires only a few minutes a day.

In conclusion, the MagNA Pure 96™ high throughput automated extraction system is a reliable device for extracting total virus nucleic acids from a broad range of clinical respiratory specimens in order to detect viruses by various real-time PCR tests. A batch of 96 samples can be extracted in less than 1 hr, which allows for very rapid molecular diagnosis and thus identification of viral pathogens. Operator time is reduced thanks to ready-to-use reagents that can be kept at room temperature. These features are all of great economic importance, in addition to providing rapid diagnosis and improving patient management.

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