Supplementary Material

Supplement 1: Further information about the cobas® Liat® point of care test

The *Roche cobas® Liat® point of care influenza A/B and respiratory syncytial virus (RSV) test* detects influenza A and B, and RSV. If a first run is unsuccessful (error or invalid is reported), the cobas® Liat® system requests the sample to be retested. The possible outcomes as displayed by the system are shown in Table S 1.

Table S 1 The range of possible results from the cobas® Liat® test as they are displayed.[1]

Assay Invalid. Repeat Assay	
Error #. Assay Aborted	
RSV	RSV Detected
	RSV Not Detected
	RSV Indeterminate. Repeat Assay.
Influenza A	Influenza A Detected
	Influenza A Not Detected
	Influenza A Indeterminate. Repeat Assay.
Influenza B	Influenza B Detected
	Influenza B Not Detected
	Influenza B Indeterminate. Repeat Assay.

In the study, repeat testing was carried out after an initial invalid, indeterminate or error occurred. Only one repeat test was carried out, regardless of its result. The repeat testing involved further dilution of the sample with universal transport medium (see Supplement 2: Procedure used for nasopharyngeal aspirate sampling and subsequent testing).

Supplement 2: Procedure used for nasopharyngeal aspirate sampling and subsequent testing

Participants were recruited from the Children's Emergency Department, Medical Assessment Unit and wards of the Great North Children's Hospital (GNCH), 08:00-16:00 weekdays, and the paediatric wards of Sunderland Royal Hospital (SRH), 08:00-16:00 Monday-Thursday.

Nasal secretions were sampled from participants by nasopharyngeal aspirate (see Box 1) flushed through with 3mls of sterile saline solution before performing the cobas® Liat® POC test. It should be noted that nasopharyngeal aspirates are not a currently indicated sample type for the cobas® Liat® POC test. The system reports the presence or absence of RSV and influenza A/B. Indeterminate, invalid and result errors are also displayed (see Table S1). If an indeterminate, invalid or error result was reported, 1.4ml of the remaining sample was added to 1ml of universal transport medium (BD Biosciences, Wokingham, UK) and

[1] RSV = Respiratory syncytial virus.

the diluted sample was immediately retested. If secondary testing reported an invalid or error result, no further testing was carried out with the POC test.

The remaining sample (1.4ml) was transported to the local virology laboratory and tested following the standard operating procedure for clinical samples (also see **Error! Reference source not found.** in main manuscript). At the time of the study, GNCH was serviced by an onsite laboratory, using the Luminex® NxTAG Respiratory Pathogen Panel and SRH sent samples to the Queen Elizabeth Hospital, Gateshead, 11 miles away, which used the Argene® RSV/hMPV r-gene™ respiratory panel. Both reference tests also detect influenza A/B and RSV.

Box 1: Standard operating procedure for sample extraction and dilution

Nasopharyngeal aspirate samples are an off-label sample type for the influenza A/B and respiratory syncytial virus (RSV) assay on the cobas® Liat® system.

Equipment required

1. cobas® Liat® analyser
2. cobas® Liat® assay pack (including pipette)
3. 0.9% saline 5ml vial
4. Suction catheter – appropriate size for child
5. Trachea suction set (mucus aspirator and trap)
6. Suction tubing
7. Hospital wall suction set at 15 – 20 KPa

Procedure

1. Remove cobas® Liat® Influenza A/B and RSV assay pack from fridge and leave at room temperature for 15 minutes
2. Check that the cobas® Liat® analyser is operational
3. Check written informed consent in place
4. Explain procedure to carers (and child if appropriate)
5. Connect suction catheter to trachea suction set and wall suction tubing
6. Introduce suction catheter aspirator in to nostril and suction for 2 seconds to obtain secretions
7. Wash through the tubing with 3mls of 0.9% saline which is collected into trachea suction set.
8. Follow Roche cobas® Liat® instructions on package insert for cobas® Liat® testing.
9. If RSV result is positive of negative, go to step 12.
   If RSV result is indeterminate or an error or invalid occurs: split the remaining sample and dilute one half (~1.4ml of sample) with 1ml of UTM[2] and immediately retest with cobas® Liat®.
10. Dispose of cartridge in biohazard waste bin as per local procedure.
11. Remaining sample to be transported to the laboratory in transport tube as per standard clinical procedure (include 'DEC-RSV' study label with form).
12. Complete all relevant paperwork

[2] UTM = universal transport medium

Supplement 3: Procedure used to analyse samples with discrepant results between point of care and laboratory test

Research nurses checked if the POC results agreed with the laboratory test results. In the event of a discrepancy, the remaining sample was sent to the laboratory at the other study centre and testing performed. The result at the other study site was considered the final arbiter (e.g. if the cobas® Liat® POC test and the laboratory test from the GNCH were discrepant, the sample was sent to the Sunderland laboratory (Queen Elizabeth Hospital, Gateshead), and the result there was considered the final sample result). Table S 2 summarises the algorithm used. If the first cobas® Liat® POC test flagged an invalid result, an error, or an indeterminate result for RSV and if a second test had been carried out, the second test result was compared.

Table S 2 Summary of method used to further analyse samples with discrepant results.[3]

cobas® Liat® point of care test result	**Laboratory test result**	**Discrepant testing required?**
RSV positive	RSV positive	no
RSV negative	RSV negative	no
RSV positive	RSV negative	yes
RSV negative	RSV positive	yes
RSV indeterminate (on second test)	RSV positive or negative	yes

	Results of tests agree, no need for further testing, remaining sample can be discarded.
	Results of tests disagree, further discrepant testing required, sample must be stored and sent for discrepancy testing.

The full protocol for the clinical study can be provided from the authors.

Supplement 4: Further details of cost analysis methodology

The data collected enabled modelling and analysis of the costs associated with the diagnosis and management of RSV for a hypothetical cohort of 1000 patients. A decision-tree model was developed in TreeAge Pro 2017 (Williamstown, MA, USA), to extrapolate the results of this study to a hypothetical cohort of 1000 patients presenting to a UK NHS hospital during the 2017/2018 winter season. The aim was to estimate cost differences between use of a POC test for RSV and standard laboratory testing, only considering decisions related to the diagnosis and management of RSV.

The model assumed (a) that all patients have a respiratory sample taken upon admission to a paediatric ward or department, (b) that if the cobas® Liat® POC test was positive for RSV, the clinical team would manage the child in single room isolation and invoke barrier nursing precautions, and (c) that if the cobas® Liat® POC test was negative for RSV, the patient would be managed in a general paediatric bay without barrier nursing (unless there was clinical suspicion of another infective cause for the patient's

[3] RSV = respiratory syncytial virus.

symptoms). If the POC test failed (10% failure rate as observed in the study), then the patient would be managed by standard practice. The comparator was standard practice where decisions regarding patient management are made on the basis of clinical symptoms while awaiting the results of the laboratory-based test result.

The cost outcomes were expressed as a total cost per cohort of 1000 patients and as the time frame is less than one year, no discounting of costs or outcomes was performed.

Table S 3 shows the study recorded prescription rates of the common antibiotics used for the participants of the DEC-RSV study. Table S 4 shows the treatment costs per pack of each antibiotics.

The estimated cost and health consequences of transmission of RSV to other patients in the hospital were not included.

The parameters and ranges for the sensitivity analyses were quantified with frequency and usage data from the study, drug costs from British National Formulary(1) and Monthly Index of Medical Specialities (MIMS)(2), isolation costs from the Health Protection Scotland(3) and NHS Reference costs(4) (see Table S 5).

We assumed that the laboratory tests were 'gold standard' i.e. 100% sensitive and specific, therefore no misclassification of results was modelled. Thus, our model is a conservative estimate of the effects of introducing the new test into the current pathway.

Table S 3 Antibiotic treatment for patients with acute bronchiolitis. Source - The DEC-RSV Study.

Antibiotics most commonly prescribed	**% prescribed**
Amoxicillin	60%
Cefuroxime	0%
Co-amoxiclav	8%

Table S 4 Treatment costs

Parameter name	**Base case value (cost per pack)**	**Description of parameter**	**Year of estimate**	**Dosage**	**Source**
c_amox	125mg/5ml oral susp, 100ml=£1.46.	cost of amoxicillin (oral suspension)	2017/2018	40 mg/kg	British National Formulary(1), MIMS online(2)
c_cefurox	250mg vial = £0.94	cost of cefuroxime - IV use	2017/2018	0-3 months (not recommended), 3-24 months 10 mg/kg 2x per day	British National Formulary(1), MIMS online(2)
c_coamox	125/31mg per 5ml, 100ml=£5.00	cost of co-amoxiclav (oral suspension)	2017/2018	0-11 months 0.25 mL/kg, 3 x per day, 12-24	British National Formulary(1),

				months 5 mL, 3x per day	MIMS online(2)

Table S 5 Quantification of model parameters and ranges for sensitivity analyses.[4]

Description of parameter	**Base case value**	**Source**	**Range for sensitivity analysis**
Average number of days in hospital	1.9 days	The DEC-RSV study	50% - 150% of base case
Cost of antibiotics	£1.29	BNF, MIMS online (1, 2). Frequency of use data from DEC RSV study. See Table S 3Table S 4	NA
Cost of barrier nursing, gowns and gloves	£22.63	Health Protection Scotland, 2011 (3) (inflated to 2017/2018)	50% - 150% of base case
Cost of a Day in a cohorted Ward	£475.16	NHS Reference Costs 2014/2015 (inflated to 2017/2018) (4)	50% - 150% of base case
Cost of day in isolation	£577.62	Health Protection Scotland, 2011 (3)	50% - 150% of base case
Probability of antibiotic prescription	0.342	The DEC-RSV study	NA
Probability of using barrier nursing, gowns and gloves	1.00	The DEC-RSV study	0.0 - 1.0
Prevalence of RSV[5] in cohort	0.57	The DEC-RSV study	0.0 - 0.75
Prevalence of other viruses from DEC RSV study	0.27	The DEC-RSV study	0.0 - 0.5
Sensitivity of POC test	1.00	The DEC-RSV study	0.921 - 0.997
Specificity of POC test	0.9853	The DEC-RSV study	0.96 - 1.0
Average time to obtain standard laboratory result (days)	1.24 days	The DEC-RSV study	50% - 150% of base case
Average time to obtain RSV result from POC test (days)	0.025 days	The DEC-RSV study	50% - 150% of base case

[4] RSV = respiratory syncytical virus, POC = point of care, MIMS = Monthly Index of Medical Specialties, NA = not applicable

POC test failure rate	0.10	The DEC-RSV study	50% - 150% of base case

Supplement 5: Discrepancy resolution results

Discrepancy resolution testing was indicated for two samples from GNCH and 3 from SRH. The results following discrepancy resolution are shown in Table S 6.

GNCH

- One sample tested positive for RSV on the cobas® Liat® test (successful on first attempt) and negative for RSV (and all other viruses) on the Luminex laboratory-based assay. The sample was sent for testing at Gateshead laboratories, using the Argene PCR Assay and RSV was detected. Therefore, an initial false positive result was re-classified as a true positive.
- One sample tested positive for RSV on the cobas® Liat® test (successful on first attempt), negative for RSV but positive for rhinovirus on the Luminex laboratory-based assay. The sample was sent for testing at Gateshead laboratories, using the Argene PCR Assay and RSV was detected (rhinovirus was not detected). Therefore, an initial false positive result was re-classified as a true positive.

SRH

- One sample tested negative for RSV on the cobas® Liat® test (unsuccessful on first attempt, repeat test required), and positive for RSV on the Argene PCR Assay. The sample was sent for testing at the Newcastle Laboratories, using the Luminex Assay and adenovirus was detected and RSV was not detected. Therefore, an initial false negative result was re-classified as a true negative.
- One sample tested positive for RSV on the cobas® Liat® test (unsuccessful on first attempt, repeat test required), and negative for RSV and all other viruses on the Argene PCR Assay. The sample was sent for testing at the Newcastle Laboratories, using the Luminex Assay and rhinovirus was detected. RSV was not detected. Therefore, this sample remained as a false positive result.
- One sample tested positive for RSV on the cobas® Liat® test (successful on first attempt) and negative for RSV (and all other viruses) on the Argene PCR Assay. This sample was not sent for further discrepant testing, as per protocol and therefore was removed from the analysis.

Table S 6 Summary of discrepant sample resolution[6]

	Number of samples
FP reclassified to TP	2
FP remaining FP	1
FN reclassified to TN	1
FP removed from re-analysis	1
Total number of discrepant samples	**5**

[6] FP = false positive, TP = true positive, FN = false negative, TN = true negative.

References

1. British National Formulary (BNF). 2018 [cited 2018 04/10/2018]. Available from: https://bnf.nice.org.uk/.
2. Monthly Index of Medical Specialties (MIMS). [cited 2018 4/10/2018]. Available from: https://www.mims.co.uk/drugs/infections-and-infestations/bacterial-infections.
3. Health Protection Scotland. National Services Scotland, NHS Scotland MRSA Screening Pathfinder Programme - Final Report Volume 2: An Assessment of the Economics, Implementation and Modelling of Universal Screening; 2011.
4. Salez N, Nougairede A, Ninove L, Zandotti C, de Lamballerie X, Charrel RN. Prospective and retrospective evaluation of the Cepheid Xpert(R) Flu/RSV XC assay for rapid detection of influenza A, influenza B, and respiratory syncytial virus. *Diagn Microbiol Infect Dis* 2015; 81: 256-258.