R-Mix cells are faster, at least as sensitive and marginally more costly than conventional cell lines for the detection of respiratory viruses

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Shell vials of R-Mix cells, a combination of mink lung cells and human adenocarcinoma cells (strains Mv1Lu and A549), were compared with conventional cell culture (CC) for the detection of respiratory viruses. CC used tubes of primary monkey kidney cells, Hep-2 and MRC5.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Respiratory specimens were taken from approximately 30% paediatric and 70% adult patients. Approximately 50% of the patients were inpatients. The vast majority of the patients were immunocompetent.

Setting
The setting was a medical laboratory situated in a secondary care centre. The economic study was carried out in the United States.

Dates to which data relate
The effectiveness data on the fresh specimens were obtained from 16 November 1999 to 24 March 2000. A separate validation study of R-Mix vials was carried out prior to the prospective study, using a series of frozen stocks of respiratory viruses from previous years. The resource use data were obtained during the same period. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was conducted prospectively on the specimen samples, on the basis of a decision model.

Study sample
A total of 396 respiratory specimens were cultured in the prospective clinical trial. No power calculations to determine the sample size were reported. All specimens received in the laboratory during the study period were included in the analysis, and were estimated using both methods. The initial study sample was justified as typical for a clinical virology
laboratory, and was thus appropriate for the clinical study question. The number of specimens (from frozen stocks) in the validation study of R-Mix vials was not reported.

Study design
The study was a single-centre prospective clinical trial in which the specimens were subjected to both methods of testing. The duration of the diagnostic procedures depended on the technological requirements of the methods. Blinding during the assessment stage was inappropriate. An additional validation study of R-Mix vials was performed using frozen specimens from previous years.

Analysis of effectiveness
The analysis of the clinical study was conducted on the basis of all specimens (intention to treat analysis). The main outcome measures were the ability to detect viruses and the turn-around time. The turn-around time was defined as the time interval between the specimen arriving in the laboratory and the final result for respiratory viruses being entered into the computer.

Effectiveness results
R-Mix enabled the detection of all 29 respiratory viruses tested in the validation study. This included 5 different clinical isolates of influenza A, 3 of influenza B, 7 of parainfluenza (types 1 to 3), 5 of RSV, and 9 of adenoviruses.

In the prospective clinical trial, R-Mix detected 21 viruses while CC detected 19.

There were 9 false negative specimens in the CC and 7 in the R-Mix cell culture. Of the latter 7, 4 specimens were from children. Four specimens grew influenza A by the CC, two grew RSV and one grew parainfluenza 3.

Forty-six (12%) of the 396 specimens had R-Mix coverslips that stained positive with the screen but were subsequently negative with the monoclonal antibodies ("screen positive/type negatives").

These 46 specimens had alternative testing, such as CC, direct fluorescent antibody screening for respiratory viruses, or enzyme linked immunoassay for influenza A and/or RSV.

Twenty-four of the 46 specimens were positive by alternative testing, but only 3 by the CC method (two influenza A and one RSV). Of the remaining 21, 9 were positive for influenza A and 12 were positive for RSV.

The turn-around time by R-Mix was 1.4 days for all positive specimens (60% of all positive specimens were detected on day 1), and 2 days for all specimens.

The turn-around time by CC was 5.2 days for all positive specimens and 9.8 days for all specimens.

Clinical conclusions
R-Mix could support the growth of all the respiratory clinical viruses from the frozen clinical isolates. R-Mix was at least as sensitive as CC and, for positive specimens, R-Mix was 3.8 days faster in detecting respiratory viruses in fresh clinical specimens.

Modelling
It would seem that the costing has been performed on the basis of a decision tree model.

Measure of benefits used in the economic analysis
No measure of benefit was used in the economic analysis. The study was therefore a cost-consequences analysis.
Direct costs
The costs were analysed from the perspective of the health care provider. The list prices were used for the reagent and supply costs. It was assumed that CC for the respiratory viruses required one tube of Hep-2 and two tubes of primary monkey kidney cells per specimen, while R-Mix required two shell vials per specimen. The technologist's time was estimated from the accumulation of individual jobs, which were directly observed and timed. It was assumed that a technologist costs $20 per hour.

The time calculations for R-Mix, based on the rates of events observed during the study, made the following assumptions:

8% positive samples;
12% screen positive/type negative; and
a turn-around time of 1.5 days with 60% of the positive specimens detected by day 1.

For CC, the assumptions were:

8% positive samples;
no specimens were cytopathological effect/haemadsorption positive/type negative;

screening fluorescent antibody testing was unnecessary (with the exception of haemadsorption-positive specimens, which had both influenza and parainfluenza testing, only monoclonal typing was performed);

of the viruses detected, 70% were first identified by cytopathological effect and 30% with haemadsorption;

a turn-around time of 5 days for positive specimens; and

it was necessary to filter 50% of the tubes because of contamination with bacteria or yeast.

Discounting was unnecessary, as the duration of the intervention was less than a month.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were considered in the analysis.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were carried out.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The costs were analysed using a decision model and were not treated stochastically. The total cost of the methods was
$18.79 for R-Mix and $16.66 for CC, a cost of $2.13 (11%) more per specimen for R-Mix.

The total cost of R-Mix included the costs of the shell vials ($5.50 per specimen), fluorescent antibody reagents ($7.81 per specimen), and the technologist’s time (approximately 16.6 minutes or $5.48 per specimen).

The total cost of CC included the costs of the cell lines ($7.55 per specimen), fluorescent antibody reagents ($0.35 per specimen), guinea pig red cells ($1.24 per specimen), and the technologist’s time (approximately 22.8 minutes or $7.52 per specimen).

Synthesis of costs and benefits
Not applicable.

Authors’ conclusions
R-Mix enabled the rapid identification of all the frozen virus stocks representing the seven major respiratory viral groups. When compared with CC, R-Mix was slightly more sensitive and more expensive than three cell lines (four tubes) used in CC, but it was faster by several days.

CRD COMMENTARY - Selection of comparators
The authors justified their selection of CC as a comparator on the grounds that it was the conventional current practice in their laboratory. You should decide whether the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis used a clinical trial in which all of the specimens were tested with both methods. This was appropriate for the study question. It also enhanced the validity of the results through the elimination of potential biases and confounders. The study sample was representative of the study population. It is unclear whether the sample size was sufficient to permit credible differentiation between the R-Mix and CC methods, or to identify whether the variety of viruses presented had influenced the effectiveness results reported.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

Validity of estimate of costs
All the categories of costs relevant to the health care provider were included in the analysis. The major costs and categories were reported separately. The cost analysis was conducted on the basis of a decision tree model, and no statistical analysis of the quantities and/or costs was conducted. The date to which the prices referred was not reported. No sensitivity analyses were performed, and the uncertainty associated with the results was not investigated. These features tend to weaken the generalisability of the results to other settings.

Other issues
The overall study question addressed only the diagnosis-related medical problem. The relative costs and benefits associated with the quicker detection of viruses due to the R-Mix method were not investigated.

The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability to other settings was addressed. The authors pointed out that the time estimates associated with the technician’s time could vary from laboratory to laboratory. The authors did not present their result selectively and acknowledged some further limitations of their study. For example, not exploring the additional benefit of using a third R-Mix cell vial. In addition, the detection of rhinoviruses, which can cause a significant number of respiratory infections, was not
investigated.

**Implications of the study**
The authors recommend and plan to replace CC (Hep-2 and two primary monkey kidney cell lines) with R-Mix for the isolation of respiratory viruses. They also plan to inoculate a third shell vial of R-Mix, in order to eliminate the labour-intensive step of scraping the coverslip monolayer of R-Mix at 48 hours for negative specimens.

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