Cost-effectiveness of Respiratory Syncytial virus Infection (RSV) Prophylaxis with Palivizumab in Preterm Infants in Colombia

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Abstract

***Introduction**: Respiratory syncytial virus (RSV) affects children of every age, but has more serious consequences in premature infants. The aim of this study is to assess the cost-effectiveness of palivizumab for RSV prophylaxis in premature infants (< 35 weeks) in Colombia.*

***Methods**: We designed a decision tree model comparing palivizumab against no prophylaxis, from the Colombian healthcare system perspective, with two different time horizons: acute infection phase and lifetime follow up. Effectiveness outcomes considered were deaths avoided, hospitalizations and asthma cases averted, as well as quality adjusted life years (QALYs) gained.*

***Results**: In our base case scenario, incremental cost-effectiveness ratio per QALY gained is, in Colombian pesos for 2011 (and USD at 1847 COP per UD) COP$53,121,137 (USD28,761). Costs per asthma case, death and hospitalization averted were $642,531,397 (USD347,878), $1,941,872,667 (USD1,051,366) and $134,024,954 (USD 72,564), respectively.*

***Discussion**: Palivizumab is not a cost-effective intervention in the Colombian context. To be cost-effective the cost of the medication should be decreased to two thirds of the current price.*

Resumen

***Introducción**: El virus sincitial respiratorio (VSR) afecta a niños de toda las edades, pero tiene consecuencias más serias en los prematuros. El objetivo de este trabajo es evaluar la costo-efectividad de palivizumab para la profilaxis del VSR en recién nacidos menores de 35 semanas en Colombia.*

***Métodos**: Se diseñó un árbol de decisión para comparar palivizumab con no profilaxis, desde la perspectiva del sistema de salud colombiano, empleando dos horizontes temporales: la infección aguda o toda la vida del paciente. La efectividad fue evaluada en costo por muerte evitada, hospitalización evitada y casos de asma evitados, así como en años de vida ajustados por calidad ganados (AVAC).*

***Resultados**: En nuestro caso base, la razón de costo efectividad incremental por AVAC ganado fue $53.121.137. El costo por caso de asma, muerte y hospitalización evitados fue $642.531.397, $1.941.872.667 y $134.024.954, respectivamente.*

***Discusión**: Palivizumab no es una intervención costo-efectiva en el contexto colombiano. Para que fuera costo-efectiva el costo de la medicación debería disminuirse a dos terceras partes- de su precio actual.*

Keywords: Palivizumab, Respiratory syncytial virus, Preterm infants, Cost-effectiveness analysis, Asthma
Palabras clave: Palivizumab, Virus Sincitial Respiratorio, Recién Nacidos Prematuros, Análisis de Costo-Efectividad, Asma
Clasificación JEL: I120, I18, I13

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I. Introduction

Respiratory syncytial virus (RSV) infection in healthy children usually resolves spontaneously. In premature infants, however, it can cause serious pulmonary involvement, requiring hospitalizations and intensive care (Smyth, 2006). No consensus has been reached on the causal relationship between RSV infection and long-term consequences, though some observational studies have associated RSV with asthma, allergies and chronic lung diseases (Çalışkan, 2013; Krishnamoorthy, 2012). In non-tropical regions like Colombia there is significant underreporting of upper respiratory infection. Data from the Instituto Nacional de Salud (2010), however, have reported RSV as an endemic infection, with an epidemic peak between March and July. Recommendations of the Colombian Association of Neonatalologists, therefore, suggest the use of palivizumab throughout year (Piñeros *et al.* 2012).

There is only one clinical trial (Andabaka 2013), published in 1998 (IMpact Study), designed to test the effectiveness of palivizumab in preterm infants (< 35 weeks) with and without chronic lung disease. The IMpact study was randomized, double-blind, and included 1502 infants. The dose used was 15 mg / kg, monthly, for five months. The primary outcome was number of hospitalizations for confirmed RSV infection, with a follow-up of 150 days since birth. This study found a 55% reduction in hospitalization rate (placebo 10.6% vs. palivizumab 4.8%); in the subgroup of patients with bronchopulmonary dysplasia (BPD) this reduction was 39% (12.8% placebo; 7.9% palivizumab); when the analysis excluded patients with BPD reduction was 78% (placebo 8.1%, palivizumab 1.8%). There was a difference in mortality (1% on placebo and 0.4% in the palivizumab group) but it did not reach statistical significance.

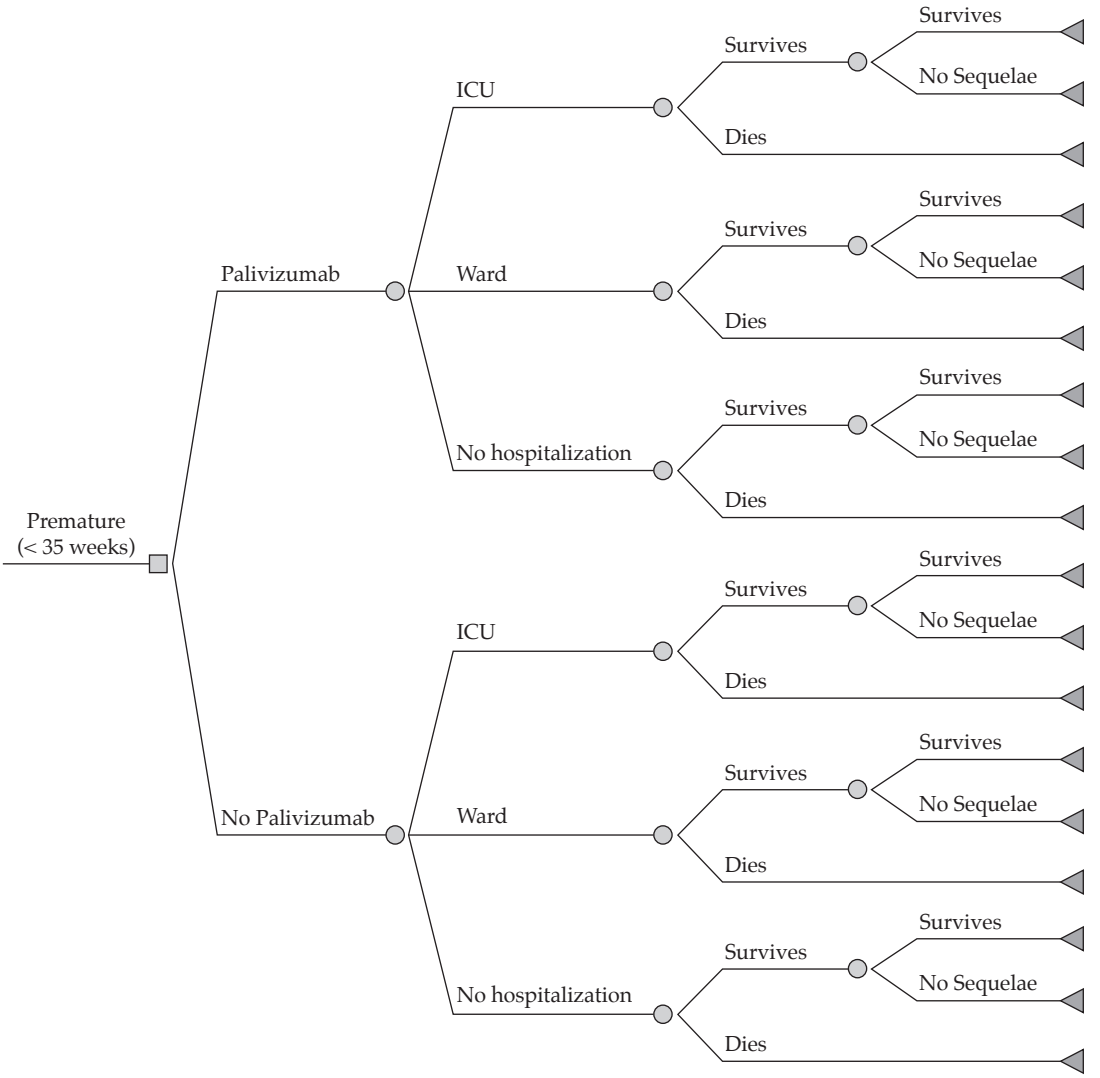
According to a report of the Observatorio del Medicamento (run by the Colombian Medical Federation), palivizumab represented in 2008 a total direct cost for the Colombian health system of COP$ 18,343,493,126 (US$9.3 million, at average official exchange rate for that year) without including "special regimes" (the Military, for example) or private payers. These reasons led the Ministry of Health and the National Guideline for Integral Attention of Preterm Infants Study Group to commission this economic analysis, and to establish cost-effectiveness of palivizumab in Colombia.

II. Materials and methods

We designed a decision tree model using TreeAge Health Pro® software (see Figure 1). Clinical information was mostly obtained from the literature, while costs were local. General population statistics were obtained from DANE (life expectancy at birth, total population and annual number of infants less than 35 weeks, discriminated according to gestational age). We used a third party payer perspective

(Colombian health care system) to compare the use in preterm infants (< 35 weeks) of palivizumab against no intervention. The simulation included two different time horizons, one for the acute phase of the condition, in which case we used the same follow-up of the IMpact-RSV Study (which was 150 days), and the other one accounting for the plausibility of palivizumab protecting against the development of asthma later in childhood (Çalışkan-, 2013). In this case we used a whole lifes-

Figure 1
GENERAL STRUCTURE OF THE MODEL



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pan time horizon. To adjust for time preferences we used three different discount rates 3%, 5% and 10%, annual discount rate both for future costs and consequences. Effectiveness outcomes considered were deaths avoided, hospitalizations and asthma cases averted as well as quality adjusted life years (QALYs) gained.

A. Review of the literature

Following Cochrane methodology for systematic reviews of the literature, we performed a systematic search to look for effectiveness and safety outcomes, as well as for economic analyses, in the following databases: Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EDD), MEDLINE, EconLit (CSA), EMBASE, Health Business Fulltext Elite and LILACS. Annex 1 shows the search strategy for PubMed (MEDLINE), in other databases an adaptation was done as required. The search was conducted between 27 and 29 July 2011.

After removing duplicate results, we had 644 abstracts that were analyzed separately by two reviewers (JDR-DR) excluding those that were considered irrelevant; 35 economic analyses were reviewed in full text, in order to select the most appropriate effectiveness and safety outcomes. Palivizumab was rendered cost-effective in 20 of these studies; 12 considered it was not cost-effective; and 3 showed variable results depending on different scenarios. Economic analyses were heterogeneous, and results were clearly dependent on the prevalence of RSV, the costs of treating the complications of RSV, the cost of the drug itself and the threshold used in decision making (Andabaka 2013).

B. Effectiveness and safety information

We used the figures reported in the IMpact RSV trial to estimate hospitalization rate. For mortality we used data from Sampalis *et al.* (2003) who studied 2415 preterm infants (32-35 week gestation) hospitalized with proven or probable RSV infection, they found mortality was 8.1%. Given the IMpact RSV hospitalization rate for placebo (10.6%) and for palivizumab (4.8%) we estimated an adjusted mortality rate of 0.86% for placebo and 0.39% for palivizumab. These results are similar to the non-statistically significant differences in mortality reported in the IMpact-RSV study (1% for placebo, 0.4% for palivizumab). In the whole lifespan horizon we used 73.2 year life expectancy based on official Colombian figures for 2012.

To simulate the possible reduction of asthma cases, we used the national Colombian prevalence estimate of 10.4% in the general population obtained by Dennis et al in 2004. Due to the safety of the medication reported in the IMpact-RSV study, similar to that of placebo, we did not include any adverse event in our model. Table 1 shows all the clinical and epidemiologic variables used in the model.

Table 1

MAIN VARIABLES USED IN THE MODEL WITH THE DISTRIBUTION USED FOR THE PROBABILISTIC MODEL

Value	Palivizumab	Control	Distribution	Reference
Hospitalization rate	4.8%	10.6%	Uniform	IMpact-RSV study
Hospitalization rate with BPD	7.9%	12.8%	Uniform	IMpact-RSV study
Hospitalization rate without BPD	1.8%	8.1%	Uniform	IMpact-RSV study
Mortality rate due to RSV	8.1%	8.1%	Uniform	Sampalis *et al.*
Mortality rate IMpact study	4.0%	10.0%	Uniform	IMpact-RSV study
Mortality rate adjusted by hospitalization rate	0.39%	0.86%	Uniform	Adjusted from Sampalis *et al.*
Mortality rate adjusted by hospitalization rate in patients with BPD	0.64%	1.04%	Uniform	Adjusted from Sampalis *et al.*
Mortality rate adjusted by hospitalization rate in patients without BPD	0.15%	0.66%	Uniform	Adjusted from Sampalis *et al.*
Mortality rate	1.58%	1.58%	Uniform	Sampalis *et al.*
Palivizumab doses by season	4.96	NA	Fixed	Fosyga reimbursment database for the years 2006-2011
Lenght of stay in ICU	1.48	1.48	Gamma	Figueras- Aloy *et al.* IMpact study the value was similar 1,37 days
Lenght of stay in ward	7.88	7.88	Gamma	Figueras-Aloy *et al.* IMpact study the value was similar 6,47
Lenght of stay in ICU in patients with BDP	2.9	2.9	Gamma	Greenough *et al.* 2001
Lenght of stay in ward in patients with BDP	39.8	39.8	Gamma	Greenough *et al.* 2002
Asthma prevalence in general population	10.4%	10.4%	Uniform	Dennis *et al.* 2004

Source: Author's calculations.

C. Resource use and costs

This evaluation included only direct medical costs. The measurement units were 2010 Colombian pesos (COP). We applied an annual discount rate of 3% for both costs and health benefits following the recommendations of the Methodological Guide of the Ministry of Health and Social Protection[1] as well as international guidelines.

To establish the number of vials used per patient, we used Fosyga database, with information collected between October 2006 and September 2011. During this period, there were 5249 claims for palivizumab reimbursement for a total of 26 036 vials, which leads to an average of 4.96 vials per patient.

Cost analysis requires three processes defined as (Drummond et al, 2005): a). Resource

[1] http://www.iets.org.co/manuales/Manuales/Gu%C3%ADa%20Econ%C3%B3mica%20revisi%C3%B3n%20v11-4-07-2013.pdf

identification: What resource use is likely in a program or treatment? This refers to listing and grouping resources into categories; b). Measurement: Refers to what amount of resources could be used in a program or treatment?; and finally c). Rating: What is the monetary value of those resources used?

For the first two steps, we used clinical protocols and clinical guidelines and reviewed bills and medical records from a convenience sample of three third-level university hospitals in Bogota (one public, two private). These records were used to estimate resource use, but their costs were not taken into account. Subject matter experts as well as the Guide Development Group (GDG) validated the results of this exercise. For the assessment of costs, we used national databases and tariff manuals and interviewed payers from Gestarsalud. The institutions that participated in the definition of the tariffs represent 34% of affiliates to contributive regime and 38% of subsidized regime.Based on this information, the members of the economic teams from the three universities (Universidad Nacional, Universidad de Antioquia and Universidad Javeriana) agreed to use rates from the Institute of Social Security (ISS) tariffs for the year 2001, with an additional 30% as the most common (and probable average) of national negotiations between insurers and providers.

The databases used to extract costs were the Integrated Information System of Social Protection (SISPRO) and the Drug Price Information System (SISMED) both run by the Colombian Ministry of Health[2]. These reports are actualized quarterly; SISMED provides information on the behavior of drug prices in Colombia through data provided by laboratories, wholesalers, insurers and providers on their sale or purchase of medications.

For the specific cost of palivizumab, this price was established by Resolution 3470 of 2011 of the Ministry of Health. The cost per milligram is $ 25,831, and the dose is 15 mg per kilogram body weight. To estimate the cost per patient in the model, we proceeded as follows: for infants less than 32 weeks, three 50 mg vials were used (one per month) and from the fourth month two vials would be required due to weight gain. In children aged 32 to 35 weeks, the first application would be of one vial, and afterwards two vials would be required. This scenario assumes that, after the application of 15 mg per kilogram body weight, the rest of medication is wasted. In a separate analysis, we assume a 20% waste reduction of the drug (combining several infants in one day, for example).

Costs were estimated in Colombian pesos for the year 2011. We used a linear distribution for costs of procedures (hospitalization, per diem in intensive

[2] http://web.sispro.gov.co/WebPublico/SISMED/LibroVirtual/index2.html

care, medical visits) with an inferior limit of ISS 2001 + 25% and an upper limit of ISS 2001 + 48%. For costs of asthma we assumed a gamma distribution, using as average costs the data reported by Hinestrosa et al (2010), who reported annual costs by age ranges: <1 year ($3,862), 2-11 ($151,697), 12-18 ($47,419), 19-45 ($66,515), and 46 and over ($28,322). These annual costs account for a total non-discounted lifetime costs of $4,309,512 per asthma case ($2,292,318, $ 1,723,546 and $ 1,081,450 for a discount rate of 3%, 5% and 10%, respectively).

D. Quality of life (utility)

Utilities were estimated using QALYs (quality adjusted life-years), taken from Greenough et al (2004) who calculated them using HUI2 (Health Utility Index 2). This measure was obtained with a 15-item questionnaire applied to parents of premature infants. The utility assigned to children with RSV was 0.88, which was lower than that of premature without RSV (0.95). For asthma we used 0.93, taken from Berg and Lindgren (2008), which was applied for the whole lifetime. The maximum threshold for an adjusted life year (QALY) gained was defined as three times GDP per capita (Eichler 2004), which in the case of Colombia, for 2012, would be $ 36 million pesos.

E. Sensitivity analysis

We performed both deterministic and probabilistic sensitivity analyses, which included 1000 Monte Carlo simulations for each one of the scenarios described below.

F. Model assumptions

The first assumption of the model is that patients with RSV infection who are hospitalized in Colombia have demographic characteristics similar to those presented in the study IMpact-RSV, and that the effectiveness of interventions and hospital stays are also similar. Another assumption is that Colombian utilities weights are similar to international published literature.

G. Scenarios

Since there is uncertainty on many variables used in this model, we tested different scenarios. All have in common infants less than 35 weeks of gestational age (information on the Impact-RSV trial does not present gestational age differences, for subgroup analysis). Our base case scenario considers patients either with or without BPD. Asthma was assumed as causally related to RSV infection, and the time horizon was the whole lifespan of the premature baby.

In other scenarios we varied the time horizon (short horizon based on the follow-up of the Impact trial, *i.e.*: 150 days; or long horizon considering asthma affecting a proportion of patients along the whole life expectancy), and the subgroups of patients (either with BPD, without BPD or the whole population of premature infants with and without BPD).

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III. Results

Base case scenario. Table 2 shows the main results for our base case scenario. The ICER per QALY gained was $53 million, $79 million and $147 million depending on the discount rate (3%, 5% and 10%, respectively). Only under a 0% discount rate the ICER is below the 3 times per capita GDP threshold. If we assume a reduction in waste (20% reduction of total milligrams employed, assuming, for example, several patients in the same day) the ICER per QALY gained would be $42,310,630. Other calculations in Table 3 show that we would be paying $643 million for every asthma case prevented (accepting the not yet proven causal relationship between RSV and asthma) or $1.9 billion per death averted (accepting the non-statistically significant difference found in the Impact Study). Finally, under these assumptions, with palivizumab applied to every preterm infant, the Colombian

Table 2

PRINCIPAL RESULTS WITH THE DIFFERENT DISCOUNT RATES

	Total cost ($)	Incremental QALY	Incremental cost ($)	Incremental effectiveness	ICER ($)	Discount (%)
Palivizumab	9,761,850	718.515	8,708,726	0.3953	22,030,675	0
Control	1,053,124	714.562				
Palivizumab	9,532,588	298.873	8,738,427	0.1645	53,121,137	3
Control	764,16	297.228				
Palivizumab	9,467,287	200.830	8,746,143	0.1105	79,150,615	5
Control	721,14	199.725				
Palivizumab	9,393,567	108.171	8,754,854	0.0595	147,140,403	10
Control	638,71	107.576				

Source: Author's calculations.

Table 3

INCREMENTAL COST EFFECTIVENESS RATIO FOR THE BASE CASE SCENARIO

	Total cost	Asthma cases x 1000	Death x 1000	Hospitalizations x 1000	ICER
Palivizumab	9,532,588	115	8	41	
Control	764,16	128	12	106	
ICER	642,531,397	1,941,872,667	134,024,954		

Source: Author's calculations.

healthcare system would be paying $134 million per hospitalization averted.

Threshold analysis. With a cost per vial of 50 mg of $ 882,689 (68.3% of the current price) the ICER of palivizumab would equal the threshold of $ 36 million. Another variable that influences the results is mortality rate of infants hospitalized for RSV. If mortality for RSV infection is 13% (instead of 8.1%), palivizumab would reach the threshold of $ 36 million per QALY gained (assuming the same relative risk reduction as a measure of effectiveness).

Other scenarios. If we analyze only the 150 day time horizon, the ICER per death averted will range from $1.87 billion to $2.32 billion (see Table 4); on the other hand, the cost per hospitalization averted would range from $139 million to $180 million.

Subgroup analysis. Unfortunately, the Impact study does not provide data for infants with different gestational ages, but provides information for patients with or without BPD.

A. Sensitivity Analysis

In a probabilistic sensitivity analysis, the probability of palivizumab being cost-effective (as determined by the threshold of $ 36 million per QALY) is less than 20%, when all the variables are modified simultaneously.

IV. Discussion

This economic evaluation has several limitations. Our literature review is based on a single trial, the IMpact-RSV, published in 1998. This, however, proves to be a limitation in the effectiveness of the medication more than of the model itself. Some of the data used in the model, as the causal association with asthma, comes from observational studies that have been questioned. Furthermore, Colombian epidemiological data of incidence, seasonality, mortality and hospitalization rates are poor.

Although cost data, which were obtained locally, may be inaccurate, the sensitivity analysis

Table 4

INCREMENTAL COST EFFECTIVENESS RATIO FOR DEATH AVERTED AND HOSPITALIZATION AVERTED, TAKING INTO ACCOUNT THE PRESENCE OR ABSENCE OF B RONCHOPULMONARY DYSPLASIA

	Per death averted	Per hospitalization averted
With or without BPD	$1,867,000,000	$139,198,810
With BPD	$2,315,409,737	$179,562,388
Without BPD	$1,826,984,375	$142,247,619

Source: Author's calculations.

shows that the only critical cost factor is the model is the cost of medication.

Our estimated cost per QALY in the baseline scenario and in all the other scenarios tested is above the threshold set in advance by the group. Only in a fifth of Monte Carlo simulations the cost per QALY would be below this value. The estimated cost paid per hospitalization averted exceeds several times the cost of a hospital stay. Something similar could be said of the cost per asthma case averted in scenarios in which this possible consequence was taken into account.

In Colombia, a threshold value per life saved, has never been established, but if we convert the value found in this study (from $1,800 million to $2,300 millions) we would be paying more than $60 million per year gained. Our results are not that much different from other cost-effectiveness studies on palivizumab (Andabaka 2013). The primary reason why palivizumab prophylaxis is inefficient (or not cost-effective) is not only the high cost of administrations but it's lack of proven effectiveness on critical outcomes such as mortality or primary prevention of infection.

This study also shows the lack of information on incidence and clinical features of RSV infection in Colombia, particularly in this specific population. These variables could influence the estimated cost per QALY, and might help explain why the intervention is cost-effective in places with seasonal epidemics and higher hospitalization costs (Andabaka 2013). Our sensitivity analysis, however, shows that the cost of the drug is the cardinal factor. With all these considerations, the conclusion is that palivizumab is not cost-effective for routine prophylaxis of RSV infection in preterm infants in Colombia.

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Annex 1

SEARCH STRATEGY
(PUBMED DESCRIBES, OTHERS WERE ADAPTED AS REQUIRED)

1	Respiratory Syncytial Virus Infections/
2	Respiratory syncytial viruses/ or respiratory syncytial virus, human/
3	(respiratory syncytial vir* or rsv).tw.
4	Respiratory Tract Infections/
5	(acute respiratory infection* or acute respiratory tract infection*).tw.
6	(lower respiratory tract infection* or lrti).tw.
7	exp Bronchiolitis/
8	bronchiolit*.tw.
9	pneumonia/ or pneumonia, viral/
10	pneumon*.tw.
11	or/1-10
12	palivizumab.tw,nm.
13	synagis.tw,nm.
14	exp Antibodies, Monoclonal/
15	(monoclonal antibod* or mab or mabs).tw.
16	Antiviral Agents/
17	Antibodies, Viral/
18	or/12-17
19	11 and 18

HTA issue 3, 2011 (8 results)
HEED (28 results)
NHS EED issue 3, 2011 (27 results)
DARE issue 3, 2011 (8 results)
PEDE 1980-2009 (26 results)
Medline 1996 - 2011 (234 results)
Embase.com 1996 - 2011 (530 results)