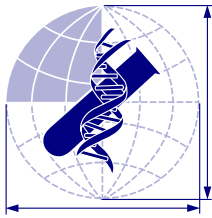


7 January 2003



Biotechnology

*Global Vaccines – Plague, Pestilence & PE's***Biotechnology**

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Highlights of this Issue

Injecting Growth

Once considered a commodity market, we forecast that the global vaccine market will achieve compound growth of 13% in the next five years.

Our global vaccine market model forecasts sales growth from \$5.4bn in 2001A to nearly \$10bn in 2006E.

Nothing to Sneeze at

The fastest growing vaccine market is for flu vaccines. We predict that this market will more than double in value to \$2bn in the next five years. Much of the forecast growth in dollar value of the flu vaccine market is expected to be driven by market entry of the premium priced FluMist product.

Babies, Beachbums, and Bioterrorists also Drive Growth

Pediatric vaccines is the biggest vaccine market, worth \$2.5bn in 2001, and specialist pediatric vaccines have blockbuster potential.

As more people travel to exotic countries with endemic disease, demand for travel vaccinations will continue to increase.

Smallpox vaccines are grabbing attention as nations build stockpiles to vaccinate every citizen in the event of an outbreak.

Initiation of Coverage – European Vaccine Companies

- PowderJect (UK) - Buy
- Berna Biotech (Switzerland) - Neutral
- Acambis (UK) - Sell.

Vaccines Database

We provide a database of marketed vaccines and products in development to prevent over 25 contagious diseases.

Refer to important disclosures at the end of this report.

Merrill Lynch Global Securities Research & Economics Group
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Investors should assume that Merrill Lynch is seeking or will seek investment banking or other business relationships with the companies in this report.

Executive Summary

The global vaccines market was worth over \$5bn in 2001, and we expect the market to grow to nearly \$10bn by 2006. Key growth drivers are flu vaccines and specialist pediatric vaccines. We have also initiated coverage of three European vaccine companies: PowderJect (UK) at Buy; Berna Biotech (Switzerland) at Neutral; and Acambis (UK) at Sell.

A \$10Bn Vaccine Market in 2006

Once considered a commodity market, we forecast that the global vaccine market will achieve compound growth of 13% in the next five years.

Our global vaccine market model forecasts growth from sales of \$5.4bn in 2001A to nearly \$10bn in 2006E. In 2003, we expect the vaccines market to grow by 20%, driven by market entry of FluMist influenza vaccine and increasing demand for pediatric vaccines. In addition, we expect increasing demand from developing countries to drive volume growth of vaccines. From 2004-2006, we expect the global market to grow at about 10% per year.

■ Key Players are Large and Small

Large pharmaceutical companies Aventis, GlaxoSmithKline, Merck and Wyeth accounted for almost 85% of global vaccine sales in 2001. Aventis is the global vaccines leader, with 28% dollar market share in 2001, if we include 50% of its joint venture sales with Merck. Pediatric vaccines represent the biggest share of the market (\$2.5bn in 2001), and the pattern of pediatric vaccine distribution fits well with big pharma GP sales forces.

It is also possible for smaller companies to be successful in certain vaccine markets. PowderJect, Berna Biotech, Chiron, Solvay and Acambis together will account for almost 17% of the 2002E global vaccine market, by our estimates. For example, both the influenza vaccine market and the travelers vaccine market are controlled by fairly well established distribution networks. Smaller companies can successfully tap into these distribution networks without requiring large sales forces of their own.

Another market suited to smaller players is smallpox vaccines, a market which is characterized by a limited number of customers, i.e. national governments. And in Europe, some smaller companies can also compete effectively for market share with regional sales forces. Berna Biotech and Chiron also supply vaccines to the developing world, by selling to single government or supranational customers.

■ Attractive Competitive Environment

The global vaccines market is characterized by high barriers to entry, due to manufacturing complexity and costly clinical trials. Vaccine manufacturing involves the large scale production of biological products, a complex process which requires extensive capital investment and years of experience to master.

Clinical development of vaccines is different from drugs, because vaccines are given to healthy individuals. As a result, very large clinical trials in tens of thousands of people are required to prove adequate safety. Large trials mean increased costs and increased risks of development. In addition, manufacturing scale up must begin sooner, in order to supply product for the large phase III studies.

In addition to high barriers to entry, the vaccine market's oligopoly structure ensures an attractive pricing environment for suppliers. Many vaccines with delivery or efficacy advantages can be priced at a premium.

Influenza Vaccine Market

Flu vaccines are one of the few vaccine products that have drug-like sales growth, i.e. increasing annual sales (because individuals need to be vaccinated every year). As a result, the flu vaccine market is the fastest growing vaccine market. We expect global sales of influenza vaccines to grow from an estimated \$962mn in 2002E to over \$2bn in 2007E, at a compound five year growth rate of 16% ('03E-'07E).

Over the next few years, there are three key factors that together will contribute to the rapid growth of the global flu vaccine market, in our view:

■ Positive Policy Recommendations

US and European governments tend to continually increase their target vaccination coverage for at-risk groups. With the elderly population the biggest at-risk group, demographic changes in the US and Europe also point to growth in influenza vaccinations. In the 2000-1 flu season, the US lowered the age of the older target group from 65 to 50 years, increasing the potential market by another 40mn doses. A potential upside for the global vaccination market is if European nations also lower the age for the recommended vaccination of older individuals.

■ New Delivery Technology

Much of the forecast growth in dollar value of the flu vaccine market is expected to be driven by the 2003 market entry of the significantly higher priced FluMist product, a nasally-administered vaccine developed by MedImmune and Wyeth. About 10% of the population is needle-phobic, and pain from injection dissuades many more from having their annual flu jab. Therefore, we believe that a key factor in expanding the flu vaccine market could be the availability of alternatives to needle vaccinations.

We expect FluMist to be priced at \$41 per dose (compared to less than \$10 paid by consumers for injectable flu vaccines). As a result, we believe that FluMist penetration will be largely confined to the healthy working population. However, FluMist is also likely to be responsible for overall expansion of the US flu vaccine market, due to its marketing campaign at launch.

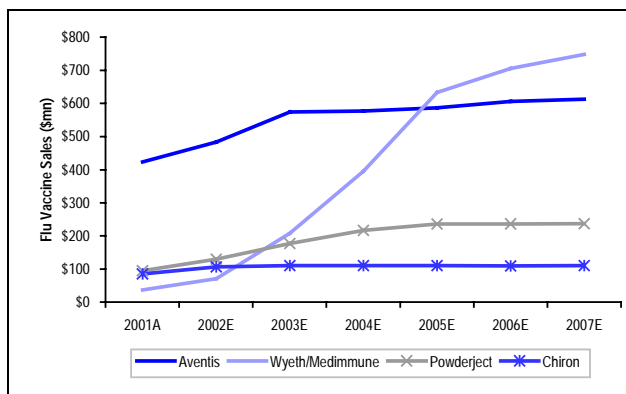
■ Developing Markets

Another key area of market expansion for influenza vaccines is the developing markets outside of the US and Europe. In the past few years, there has been significant growth in the use of flu vaccines in Central and Eastern Europe, China, Taiwan, Mexico, and Japan. The market in developing countries is mainly comprised of the affluent middle classes who can afford Western medicines. We expect these international markets for flu vaccines to expand at least at the rate of forecast GDP growth in developing countries.

■ Winners in Marketing & Manufacturing

We expect those companies with strong established links with their customers to benefit in the long term. Aventis and GSK will likely continue to generate loyalty because they supply many important vaccines in addition to flu vaccines. We also believe that the UK company Powderject will be able to maintain market share if it continues to be first into the market with the season's new flu vaccine in the US. The reliability of supply generates its own loyal customer relationships in this biggest single market for flu vaccines. We believe a similar supply advantage in Germany could allow Chiron to retain market share as well. (See Chart 1 below.)

Chart 1: Global Flu Vaccine Sales Forecasts above \$100 Million



Source: Company Data; Merrill Lynch estimates

Travelers Vaccine Market

As more people travel to countries with endemic disease, demand for vaccinations will continue to increase. From World Tourism Organization (WTO) data for 2000, we estimate that 87 million people traveled from developed countries to regions with endemic diseases. In the long term, this number is expected to grow at approximately 5% annually. However, the increase in terrorism will likely continue to cause temporary global or regional declines in tourism and travel.

The largest markets for traveler's vaccines are dominated by large pharmaceutical companies, but smaller market opportunities also exist for smaller companies. In

addition, the traveler's vaccine market presents a good marketing opportunity to increase awareness (and market size), because the majority of travelers do not take their recommended vaccinations.

Other Vaccine Markets

■ Pediatric Vaccines

The biggest single vaccine market today is pediatric vaccines, worth approximately \$2.5bn in 2001, and growing at 5%-7% per year. Children up to the age of five years are routinely vaccinated against a multitude of childhood diseases. Vaccines for measles, mumps, rubella, diphtheria, tetanus, pertussis and polio represent approximately \$1.4bn in sales.

New pediatric vaccine sales are generally characterized by a "catch-up" then "top-up" sales growth pattern. The first year or two following the launch of a new vaccine sees the highest sales revenues, as coverage is extended to all young children ("catch-up" phase). In the following years, the sales of the vaccine grows only at the birth rate as newborns are vaccinated ("top-up" phase).

Prevnar, Wyeth's pneumococcus vaccine, provides an indication of the sales potential of specialist pediatric vaccines. In 2001, Prevnar had sales of \$798mn. At about \$60 per dose, Prevnar is double the price of other branded pediatric vaccines. The price premium is supported by the vaccine's effectiveness, which was about 100% effective in prevention in large clinical studies. Although demand for the vaccine remains high, sales growth has been plagued by Wyeth's manufacturing problems. Merck recently presented remarkable clinical data for a new HPV vaccine to prevent cervical cancer, and this could become a new blockbuster pediatric vaccine.

■ Hepatitis Vaccines

Hepatitis B monovalent vaccine was the largest single vaccine market in the world in 2001, with worldwide sales estimated at over \$1bn. Hepatitis B sales have been declining globally, due to the tailing off of "catch-up" vaccination. In addition, patents covering the hepatitis B vaccine started to expire in Europe in 2002, which will likely reduce the value of the global Hep B vaccine market further, as Europe opens up to lower priced competition from the developing world. The Hepatitis A vaccine market is estimated to be worth about \$400 million. GSK, Merck and Aventis dominate. GSK's Havrix was the first to reach the market, and has been used to immunize over a million individuals to date.

■ Bioterrorism

Following the terrorist events in the US in September 2001 and the anthrax scare in October 2001, there is heightened concern that terrorist organizations may use biological agents as weapons of bioterrorism. Most attention has focussed on smallpox, a deadly disease that can only be prevented by vaccination.

US Leads in Building Vaccine Stockpiles

The US currently has enough old calf-lymph smallpox vaccine (manufactured decades ago and kept in cold storage) for 400+ million doses, enough to vaccinate every citizen in the event of a smallpox outbreak.

The US government also has contracts with the UK company Acambis and Baxter to supply 209 million doses of new smallpox vaccine, manufactured by modern cell culture methods. The two contracts are worth over \$500mn in revenues for Acambis. We expect that the US government will continue to contract supplies of smallpox vaccine from Acambis under an existing maintenance contract, so that the cell-culture vaccine eventually replaces stocks of the older calf-lymph vaccine.

Upside as Other Nations Follow Suit

Most countries outside of the US do not currently possess smallpox vaccine stockpiles sufficient to vaccinate every individual. We expect that other governments will use the same strategy as the US, i.e. (1) conduct pre-event vaccination of key “first response” health care workers, and (2) build up a stockpile of enough doses to vaccinate every individual in the event that mass vaccination is ever required. If all European countries follow the lead of the US and the UK, then we believe there could be an additional demand for 100-200 million doses or about \$300 million in potential revenues.

Most European nations previously used smallpox vaccines based on the Lister strain of vaccinia virus, so it is likely that only companies that can supply Lister-based vaccines will win new contracts, in our view.

Acambis appears to have the US smallpox vaccine market tied up, but we believe it is unlikely to make major inroads in Europe, because the Acambis vaccine is based on the NYCBH strain, favored by the US. We believe the only companies who will be able to supply smallpox vaccine to these European countries are PowderJect, Berna Biotech and Bavarian Nordic.

Initiation of Coverage: European Vaccine Companies

Separately published in-depth reports are available for the companies below.

■ **PowderJect – Buy**

PowderJect’s business is focused on two key adult markets for vaccines – flu and travel. Our research indicates that both of these areas represent good growth potential. We forecast PJP’s Fluvirin flu vaccine sales to grow from £67mn in FY02A to £157mn in FY06E, a four year CAGR of 24%. We expect PJP’s traveler’s diarrhea vaccine Dukoral to be approved in Europe in mid-CY03, and we believe that peak European sales of this drinkable vaccine could reach over £20mn by FY07E. Over the next 12-18 months, PJP also has a number of opportunities to improve its operating margins.

Combining these forthcoming operating efficiencies with Fluvirin and Dukoral sales growth, results in EPS growth of 29% CAGR (FY03E-FY06E). Our price objective for PowderJect is 514p, based on DCF analysis (12.3% WACC; 6.3x exit EV/EBITDA), representing a potential upside of 25% to the current share price, and calendarized 03E and 04E PEs of 19x and 14x, respectively.

■ **Berna Biotech – Neutral**

In 2002, Berna Biotech acquired another vaccine company Rhein Biotech. Due to restructuring charges and one-off smallpox vaccine sales in 2001, we expect that reported 2002 profits will be lower than in 2001 for the newly combined company. In addition, Berna has been plagued by manufacturing problems with its travel vaccines Vivotif and Epaxal, both of which have been recently relaunched.

Our Neutral rating reflects a valuation upside of about 15%, insufficient to justify a positive rating given the stock’s high risk, and near term uncertainties. We may become more positive when there is evidence that the travel vaccines’ franchise is back on track and Rhein successfully integrated.

■ **Acambis – Sell**

In 2000 and 2001, the US government contracted with Acambis (in collaboration with Baxter) to supply 209 million doses of smallpox vaccine. These \$500+ mn contracts should push Acambis into profitability in 2002E and 2003E.

However, we forecast that Acambis will break even in 2004 and become unprofitable again in 2005-2007. Acambis’ return to a loss-making company is caused by a revenue gap following receipt of smallpox vaccine revenues and prior to launch of any other significant vaccine products.

Our risk-adjusted sum-of-the-parts analysis gives a valuation of 220p per share, or 20% below the current share price.

We acknowledge that Acambis is likely to act as a proxy for bioterrorist risk or events, but we would be sellers into a any share price gains, because the company is fundamentally overvalued in our view. In addition, even though the smallpox contracts represent high revenue figures, the gross margin achieved is only 20%-40% (depending on the contract). We calculate that even if Acambis won another 200 million dose smallpox contract from the US government, this would represent an upside of 54p per share, which would bring Acambis in line with its current share price.

Vaccines & Diseases Database

In the Appendix of this in-depth report is database of marketed vaccines and products in development to prevent over 25 contagious diseases.

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1. Global Vaccine Market Overview

Once considered a commodity market, we forecast that the global vaccine market will achieve compound growth of 13% in the next five years. Our global vaccine market model shows growth from sales of \$5.4bn in 2001A to nearly \$10bn in 2006E. Vaccine market growth is being driven primarily by flu vaccines and specialist pediatric vaccines. High barriers to entry and pricing power should ensure an attractive competitive environment for participants in the global vaccine market.

Milk maids provided the first clue to immunity

Vaccines are Old Medicine

Vaccination was first developed in the 18th century, when it was observed that exposure to cow pox could protect individuals from contracting small pox. Immunisation was originally practiced by arm-to-arm transfer of the cow pox infection, but was replaced in the early 19th century with inoculations.

Vaccination works by priming the immune system with various forms of pathogen (bacteria or virus), so that when the live pathogen is encountered, a much more powerful immune response is launched which effectively kills the virus or bacteria without causing disease.

The herd effect benefits society

Few medicines are as effective as a powerful vaccine, and there is a broader benefit to society, because protection occurs even for unvaccinated individuals. The so-called “herd effect” results in 100% protection of the population when a significant proportion of the population is vaccinated. Infective pathogens generally require a larger pool of non-vaccinated individuals to be successfully transmitted.

... and almost \$10 billion in 2006E

A Market Worth \$6 Billion Today

In 2001, the global vaccine market was worth over \$5 billion. As shown in our global vaccine market model at the end of this section (see Table 2), we expect the market to have grown to over \$6 billion by the end of this year, and to almost \$10 billion by 2006E, a compound growth of 10% (2003E-2006E 3 year CAGR).

Pediatric and ‘flu vaccines will drive growth

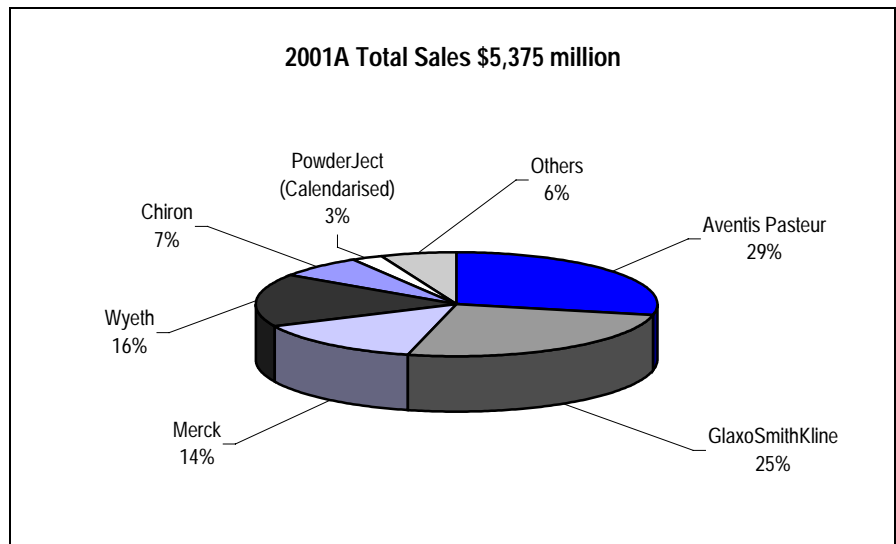
In 2003, we expect the vaccines market to grow by 20%, driven by market entry of FluMist influenza vaccine and increasing demand for pediatric vaccines. In addition, we expect increasing demand from developing countries to drive volume growth of vaccines. We understand that the total vaccines market in India is currently worth approximately \$45mn-\$50mn. From 2004-2006, we expect the global market to continue to grow at about 10% per year.

■ Key Players are Large and Small

Large pharmaceutical companies Aventis, GlaxoSmithKline, Merck and Wyeth accounted for almost 85% of global vaccine sales in 2001 (see Table 3). Aventis is the global vaccines leader, with 28% dollar market share in 2001, if we include 50% of its joint venture sales with Merck. If we only take into consideration reported sales, both Aventis and GSK had about 25% dollar market share in 2001.

Aventis is #1 in vaccines

Pediatric vaccines represent the biggest share of the market (\$2.5 billion in 2001), and the pattern of pediatric vaccine distribution fits well with big pharma GP sales forces. The largest vaccine players – Aventis, GlaxoSmithKline, Merck and Wyeth – also dominate the pediatric vaccine market.

Chart 2: 2001 Global Vaccine US Dollar Market Share


Source: Company Data; Merrill Lynch estimates

NB: Aventis Pasteur market share includes 50% sales from joint venture with Merck

It is also possible for smaller companies to be successful in certain vaccine markets. PowderJect, Berna Biotech, Chiron, Solvay and Acambis together will account for almost 17% of the 2002E global vaccine market, by our estimates.

For example, both the influenza vaccine market and the travellers vaccine market are controlled by fairly well established distribution networks. Smaller companies can successfully tap into these distribution networks without requiring large sales forces of their own. In addition, PowderJect and Chiron have made strong inroads into the US and European flu vaccine markets, respectively, by being first to market with their new vaccines for the new flu season. It can be easier for smaller companies to steal a march on their larger rivals by focusing more resources on fewer product areas.

Another market suited to smaller players is smallpox vaccines, a market which is characterized by a limited number of customers, i.e. national governments. And in Europe, some smaller companies can also compete effectively for market share with regional sales forces. Berna Biotech and Chiron also supply vaccines to the developing world, by selling to single government or supranational customers.

The full range of marketed vaccines and products in development are described in the Vaccines and Diseases database in Appendix I.

Market Characteristics

Although once considered a commodity business, the vaccine market is today an attractive business to be in. With 10% compound sales growth expected over the next five years, current market participants should benefit from high barriers to entry and pricing power.

■ High Barriers to Entry

As described above, the bulk of vaccine sales are made by only a handful of companies. The vaccines industry is characterized by high barriers to entry, so the market is likely to remain concentrated among relatively few players, in our view.

Manufacturing Complexity

Vaccine manufacturing involves the large scale production of biological products, a complex process which requires extensive capital investment and years of experience to master.

Manufacturing complexity and costly clinical trials keep out new market entrants

Most vaccines are manufactured by growing large quantities of virus in eggs or cell culture. Unlike biologic drugs, quality control in vaccines involves measuring immune response, not the activity of the compound. Immune response can be a more variable measure than activity.

In 1999, the FDA imposed new regulations for vaccine manufacturing, which brought systems in line with good manufacturing processes. Because of the more challenging regulatory environment, vaccine companies had to invest in infrastructure or withdraw from the product area. Although FDA is seen as the most strict regulatory body for vaccines, we understand that the European EMEA regulatory standards for vaccines are becoming more aligned to the FDA.

Costly Clinical Development

Unlike drugs, vaccines are given to healthy people

Clinical development of vaccines is different from drugs, because vaccines are given to healthy individuals. Therefore, the risk/benefit ratio for vaccines is different – the safety profile has to be very good. As a result, very large clinical trials are required to prove adequate safety. For example, Merck's ROTATEQ pediatric vaccine is being tested in a study of 60,000 infants.

Large trials mean increased costs and increased risks of development. Large scale safety studies can cost \$50mn-\$100mn for 50,000-100,000 people. In addition, manufacturing scale up must begin sooner, in order to supply product for the large phase III studies.

■ **Pricing Power**

The vaccine market's oligopoly structure ensures an attractive pricing environment for suppliers. In addition, specialist vaccines can command a high price premium. Wyeth's pediatric vaccine Prevnar is double the price of other pediatric vaccines, because it was shown to be 100% effective in clinical trials. Influenza vaccines also experienced large price increases in the US and the UK in the 2000-1 flu season following shortages in the previous year. Combination vaccines (the dominant form of pediatric vaccines) can also be priced at a premium because they lower the risk of patient infection and are more convenient than monovalent vaccines (less discomfort, higher compliance).

Market Risks

Key risks are manufacturing and safety concerns

Individual companies involved in the vaccine market face risks to growth mainly in the areas of manufacturing and safety concerns. Following the crack down on vaccine manufacturing in the US in 1999, most European-based companies also upgraded their manufacturing processes due to the expectation that the European authorities would also increase the stringency of their manufacturing regulations. As a result of vaccine manufacturing modernization, manufacturing risks have lessened. However, manufacture of vaccines still entails the manipulation of living organisms, so no system is risk-free.

Safety perceptions for vaccines are a large risk and needs to be carefully managed. Vaccines are administered to millions of healthy individuals, so any safety questions are not tolerated by the public or the regulators. In addition, it is very difficult to prove that a vaccine *does not* cause a particular side effect, without conducting a trial in thousands of individuals. Due to the success of vaccination, dangerous diseases are no longer a serious public health threat, so the benefit of vaccination is generally not apparent.

For example, in the UK, use of the combination MMR vaccine in children has declined, due to unsubstantiated concerns linking the vaccine to autism. In France, hepatitis B vaccines have been linked to multiple sclerosis. In the US, vaccine preservatives such as thimerosal have also been linked to autism.

Nonetheless, the fear of risks will not likely affect the overall growth of the vaccine market, because of government focus on vaccination as cost-effective healthcare.

Table 1: Global Vaccine Model – Sales Model for Major Vaccine Companies

Aventis Pasteur	(EURmn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Influenza Vaccines		188	240	473	493	585	588	599	618
Pediatric Combination Vaccines		307	370	378					
Travellers/Endemic Range		69	280	327					
Injectable Polio Vaccines		119	217	244					
Hepatitis B Products		135	118	74					
Human Vaccines		818	1,091	1,425	1,578	1,767	1,961	2,157	2,373
% Change			33.4%	30.6%	10.7%	12.0%	11.0%	10.0%	10.0%
(Sales include a proportion of sales made to Aventis Pasteur MSD 50:50 JV with Merck)									
GlaxoSmithKline	(€mn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Hepatitis (Twinrix, Havrix and Engerix-B)		480	462	445	455	432	419	419	419
Infanrix (DTP vaccine)		120	171	238	306	382	459	528	586
Others		176	209	265	341	410	483	556	639
Vaccines		776	842	948	1,102	1,224	1,361	1,503	1,644
% Change			8.5%	12.6%	16.2%	11.1%	11.2%	10.4%	9.4%
Merck	(USDmn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Hepatitis (Vaqta, Recombivax HB and Comvax)		300	345	340	324	344	360	373	386
Viral Vaccines		490	520	515	549	585	613	636	654
Rotavirus Vaccine									75
HPV Vaccine									100
Other Vaccines		70	87	167	204	197	205	213	221
Vaccines/Biologicals		860	952	1,022	1,077	1,126	1,178	1,222	1,436
% Change			10.7%	7.4%	5.3%	4.5%	4.6%	3.7%	17.5%
Sales of 50:50 JV in Europe with Aventis Pasteur:									
Hepatitis Vaccines		160	134	88					
Viral Vaccines		69	49	41					
Other Vaccines		339	358	371					
Total JV Sales (fully booked by Merck)		567	541	500	587				
Wyeth	(USDmn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Prevnar		0	460	798	584	818	938	1,023	1,096
Meningitec		49	322	79	75	72	68	65	61
FluMist					0	208	396	633	706
Total Vaccine Sales		49	782	877	659	1,098	1,402	1,721	1,863
% Change			1500.1%	12.1%	(24.9%)	66.7%	27.6%	22.8%	8.3%
Chiron*	(USDmn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Menjugate		0	115	106					
Other Vaccines		209	230	260					
Total Vaccine Sales		209	345	366	336	374	405	434	475
% Change			65.1%	6.2%	(8.0%)	11.2%	8.1%	7.2%	9.4%

Source: Merrill Lynch estimates

*Chiron estimates are consensus estimates

Table 2: Global Vaccine Model – US Dollar Sales by Company

(USDmn)	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Aventis Pasteur	871	1,005	1,275	1,647	1,845	2,047	2,252	2,477
<i>Aventis Pasteur (adjusted for JV with Merck)</i>	<i>1,154</i>	<i>1,275</i>	<i>1,525</i>	<i>1,941</i>				
GlaxoSmithKline	1,255	1,274	1,365	1,767	1,962	2,182	2,409	2,635
Merck	860	952	1,022	1,077	1,126	1,178	1,222	1,436
<i>Merck (adjusted for JV with Aventis Pasteur)</i>	<i>577</i>	<i>682</i>	<i>773</i>	<i>784</i>				
Wyeth	49	782	877	659	1,098	1,402	1,721	1,863
Chiron	209	345	366	336	374	405	434	475
Baxter	0	0	35	150	200	220	245	265
Acambis	0	0	0	117	341	151	95	111
PowderJect (Calendarised)	0	39	135	227	244	283	314	331
Berna Biotech	119	114	173	174	143	143	165	180
Rhein Biotech	53	50	69	0	0	0	0	0
Solvay	45	47	50	66	66	66	66	66
Shire Pharmaceuticals	6	7	7	9	14	18	34	35
Vaccines Market	3,466	4,615	5,375	6,229	7,413	8,094	8,956	9,875
% Change		33.1%	16.5%	15.9%	19.0%	9.2%	10.6%	10.3%

Source: Merrill Lynch estimates

Table 3: Global Vaccine Model – US Dollar Market Share by Company

Market Share	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E
Aventis Pasteur	25.1%	21.8%	23.7%	26.4%	24.9%	25.3%	25.1%	25.1%
<i>Aventis Pasteur (adjusted for JV with Merck)</i>	<i>33.3%</i>	<i>27.6%</i>	<i>28.4%</i>	<i>31.2%</i>				
GlaxoSmithKline	36.2%	27.6%	25.4%	28.4%	26.5%	27.0%	26.9%	26.7%
Merck	24.8%	20.6%	19.0%	17.3%	15.2%	14.6%	13.6%	14.5%
<i>Merck (adjusted for JV with Aventis Pasteur)</i>	<i>16.6%</i>	<i>14.8%</i>	<i>14.4%</i>	<i>12.6%</i>				
Wyeth	1.4%	17.0%	16.3%	10.6%	14.8%	17.3%	19.2%	18.9%
Chiron*	6.0%	7.5%	6.8%	5.4%	5.0%	5.0%	4.8%	4.8%
Baxter	0.0%	0.0%	0.7%	2.4%	2.7%	2.7%	2.7%	2.7%
Acambis	0.0%	0.0%	0.0%	1.9%	4.6%	1.9%	1.1%	1.1%
PowderJect (Calendarised as March YE)	0.0%	0.9%	2.5%	3.6%	3.3%	3.5%	3.5%	3.4%
Berna Biotech	3.4%	2.5%	3.2%	2.8%	1.9%	1.8%	1.8%	1.8%
Rhein Biotech	1.5%	1.1%	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%
Solvay	1.3%	1.0%	0.9%	1.1%	0.9%	0.8%	0.7%	0.7%
Shire Pharmaceuticals	0.2%	0.1%	0.1%	0.1%	0.2%	0.2%	0.4%	0.4%

Source: Merrill Lynch estimates

*Chiron estimates are consensus estimates

2. Influenza Vaccine Market

Flu vaccines are one of the few vaccine products that have drug-like sales growth, i.e. increasing annual sales. As a result, the flu vaccine market is the fastest growing vaccine market, with an estimated 16% five year CAGR ('03E-'07E). Much of the growth in dollar value of the flu vaccine market will be driven by market entry of the significantly higher priced FluMist product. We expect the number of flu vaccinations to grow at 6% five year CAGR.

A \$2 Billion Market by 2007E

We expect global sales of influenza vaccines to grow from an estimated \$962mn in 2002E to over \$2 billion in 2007E, at a compound growth rate of 16% (see ML Global Influenza Vaccine Model, Tables 4-8).

Over the next few years, there are three key factors that together will contribute to the rapid growth of the global flu vaccine market, in our view – policy recommendations, new delivery technology, and developing markets.

These three key factors are described below. However, there is a fourth factor that significantly affects the expansion and contraction of the global vaccine market in any given year, but this factor is highly unpredictable – it is the degree of severity of historic flu seasons. It is undeniable that the vaccine market will expand the year after a particularly severe flu season, and that mild flu seasons lead to some complacency in vaccination in the following years. Nonetheless, the three key factors below will contribute to underlying expansion of the global flu vaccine market, in our view.

■ Positive Policy Recommendations

Government policy is probably the biggest driver of the global vaccine market. National governments are strongly in favor of influenza vaccination, because of its attractive cost/benefit characteristics. Influenza vaccinations help save millions of dollars each year in reduced hospitalizations and fewer lost work days. In the US, 114,000 people are hospitalized and there are 20-40,000 deaths each year from influenza. During epidemics, hospitalizations and deaths from influenza can increase dramatically above these levels.

US and European governments tend to continually increase their target vaccination coverage for at-risk groups. With the elderly population the biggest at-risk group, demographic changes in the US and Europe also point to growth in influenza vaccinations.

The US Advisory Committee on Immunization Practices (ACIP, part of the CDC), recommends influenza vaccination for the following target groups:

- Individuals aged 50 years or older.
- Residents of nursing homes or chronic care facilities.
- Adults or children with chronic pulmonary or cardiovascular disorders (including asthma).
- Adults or children with chronic metabolic disorders (including diabetes), renal dysfunction, or immunosuppression requiring medical follow-up or hospitalization within the preceding year.
- Women in their second or third trimester of pregnancy.
- Healthcare workers and others (including household members) in close contact with high risk groups.

There is currently no European umbrella organization that makes recommendations for influenza vaccination; this role is left to the individual national governments. In general, however, European recommendations are

Nothing better to expand the market than a bad flu season

Demographics favor increasing flu vaccinations

similar to the ACIP guidelines with respect to adults and children with chronic pulmonary or cardiovascular disorders. European governments also recommend vaccination of the elderly (generally for those aged 65 or older), residents of nursing homes and chronic care facilities, plus those with chronic metabolic diseases, renal dysfunction, or immunosuppressive disorders. Recommendations for vaccination of healthcare workers is less common in Europe than in the US, however.

The UK is one of the more aggressive European countries in setting vaccination targets. For the current 2002-3 influenza season, the UK Department of Health (DoH) set a target of 70% among those aged 65 years and over to receive flu vaccines, an increase from the 2000-01 flu season target of 65%. In the 2001-2 flu season the UK DoH reported that 68% of over-65's had received flu jabs.

The US lowered the bar for vaccinating older people – will Europe follow suit?

In the 2000-1 flu season, ACIP lowered the recommended age for flu vaccinations from 65 years to 50 years. ACIP's rationale was that 24%-32% of 50-64 year olds have a chronic condition that places them at high risk for influenza-related hospitalization and death, and that age-based recommendations are more effective than patient selection strategies for ensuring vaccination.

Lowering the recommended age for influenza vaccinations in the US increased the potential market by an additional 40 million doses. A potential upside for the global vaccination market is if European nations also lower the age for the recommended vaccination of older individuals.

Vaccinating US toddlers could add another six million doses

For the current 2002-3 flu season, ACIP also voted to "encourage" the vaccination of healthy children aged 6-23 months, because of their increased risk for influenza-related hospitalizations. ACIP expects to pass a formal recommendation to vaccinate this target group within the next 1-3 years. This group alone would add another six million doses, and represents more potential upside for the US flu vaccine market.

■ New Delivery Technology

In our view, much of the growth in dollar value of the flu vaccine market will be driven by market entry of the significantly higher priced FluMist product, a nasally-administered vaccine.

About 10% of the population is needle-phobic, and pain from injection dissuades many more from having their annual flu jab. Therefore, we believe that a key factor in expanding the flu vaccine market could be the availability of alternatives to needle vaccinations.

Nasal flu showed the big potential of needle-free delivery

In the 2000-1 flu season, Berna Biotech launched a nasally administered influenza vaccine in Switzerland. Even though Nasal flu was launched late in the season (October) at more than 3x the price of conventional vaccines (with no reimbursement) and without a marketing campaign, it was immediately successful. Berna sold 90,000 doses of Nasal flu out of a total 1,000,000 sold in Switzerland that season (achieving 9% market share).

Nasal flu was prescribed for high risk patients as well as healthy individuals. In the latter category, a preference for nasal spray was clear, despite the price premium. In a campaign for city employees in Basle, for example, 1,641 employees were treated with Nasal flu, and only 33 opted for the injected vaccine that was also offered. According to physicians surveyed by Berna Biotech, about half of the people who were vaccinated spontaneously asked for Nasal flu vaccination.

However, Berna Biotech decided to take Nasal flu off the market following a single flu season, due to rare cases of temporary facial paralysis (Bell's Palsy). In a large post-marketing clinical trial, the Company was unable to prove that occurrence of Bell's Palsy was unrelated to vaccination with Nasal flu. Berna Biotech is developing a revised formulation of Nasal flu with Aventis.

*“Healthy worker” concept
should help expand the market*

*We expect the FluMist launch
to drive US market expansion
in 2003*

*five million doses sold in China
– and that’s just the beginning*

In our view, the Nasal flu experience in Switzerland demonstrates the potential for needle-free vaccine delivery to expand the influenza vaccine market, particularly among the healthy working population.

A key area for market expansion is the healthy working population, which is over 280 million individuals in the US and Europe. The US government is currently emphasizing a “healthy worker” concept, whereby the aim is for 50% of the working population to receive flu vaccinations, pushing cost savings to employers. Indeed, many large corporations organize flu vaccination schemes for their employees in the autumn. The “healthy worker” concept is starting to be developed in Europe as well, although it is not as advanced as in the US. For example, private healthcare companies in the UK like BUPA have started to supply flu vaccines to corporate customers.

Wyeth and MedImmune plan to launch FluMist, a nasally administered flu vaccine, into the US market for the 2003-4 influenza season. In December 2002, the FDA Vaccines Advisory Panel recommended approval of FluMist for use in healthy individuals aged 5-49 years. We expect FluMist to be priced at \$41 per dose (compared to less than \$10 paid by consumers for injectable flu vaccines). As a result of both the pricing and the FDA Panel recommendations, we believe that FluMist penetration will be largely confined to the healthy working population (see Global Influenza Vaccine Model, Tables 4-8).

However, we believe that FluMist is also likely to be responsible for overall expansion of the US flu vaccine market, due to its marketing campaign at launch. We expect MedImmune and Wyeth to spend \$30 million on launch marketing in the 2003-4 flu season, compared to an annual average of less than \$3 million total spent on marketing flu vaccines in the US. The FluMist marketing message is likely to emphasize the serious risks associated with influenza infection, which we believe will increase awareness of influenza vaccination in high risk target groups such as older individuals.

■ Developing Markets

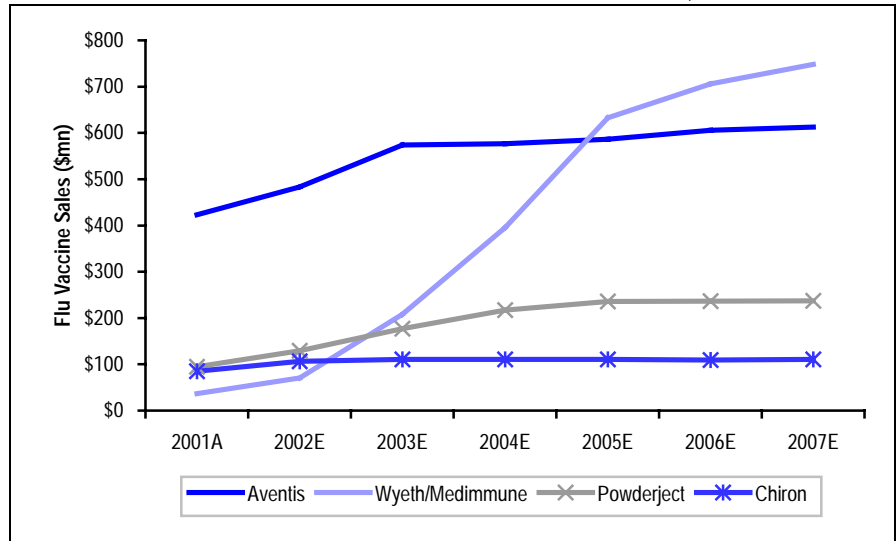
Another key area of market expansion for influenza vaccines is the developing markets outside of the US and Europe. In the past few years, there has been significant growth in the use of flu vaccines in China, Taiwan, Mexico, Japan and in Eastern Europe.

For example, in the 2001-2 flu season, approximately five million doses were sold in China, at only a slight discount to European prices. The market in developing countries is mainly comprised of the affluent middle classes who can afford Western medicines. We expect these international markets for flu vaccines to expand at least at the rate of GDP growth in developing countries.

Global Model & Market Dynamics

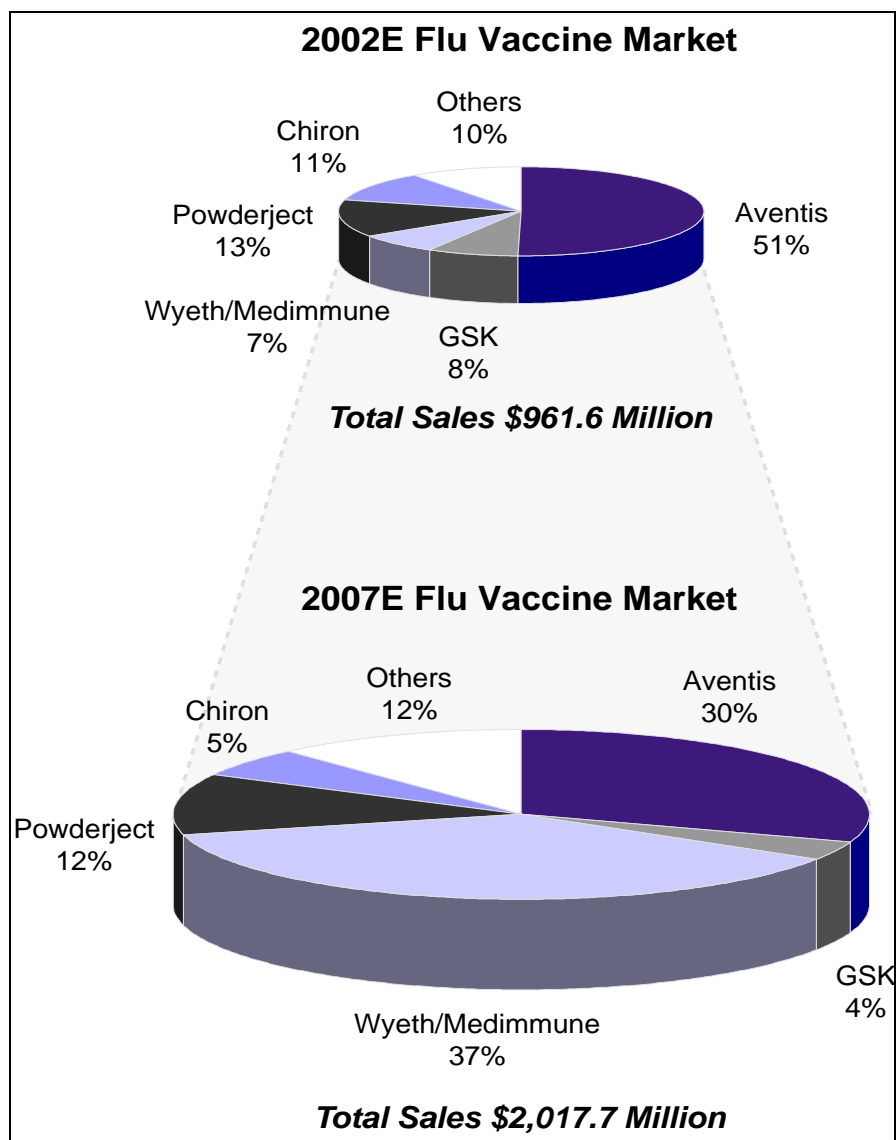
The Merrill Lynch Global Influenza Vaccine Model is shown in Tables 4-8. We estimate that the global flu vaccine market will grow from an estimated \$962mn in 2002E to over \$2 billion in 2007E, at a compound growth rate of 16%. Much of the growth in dollar value of the flu vaccine market will be driven by market entry of the significantly higher priced FluMist product. The charts below indicate how we expect market share among the global flu vaccine players to develop between 2002E and 2007E.

Chart 3: Global Flu Vaccine Model – Product Sales Forecasts above \$100 Million



Source: Company Data; Merrill Lynch estimates

Chart 4: Global Flu Vaccine Market



Source: Merrill Lynch estimates

Vaccination of key target groups should grow at 5% per year

An upside would be a move to vaccinating 50+ year-olds in Europe

Emerging regions to see 5%-10% annual growth

Healthy workers will be the key target market for FluMist

■ Underlying Growth from Increased Vaccination of Target Groups

In our global flu vaccine model, we forecast market growth based on increased penetration of several target populations in the US and Europe: the older population, the at-risk population, and healthcare workers. We have increased penetration rates to reflect the eventual achievement of government targets. In our global model, the underlying growth of influenza vaccinations among target populations is 6% CAGR ('03E-'07E).

CDC data state that in the 1999-2000 flu season, the following coverage rates were achieved for flu vaccination in target groups: 52% of all individuals 50 years and older; 21% of at-risk individuals, and 47% of healthcare workers. Following the shortages of vaccine in the 2000-1 flu season, CDC data suggest that coverage rates of target groups were down 4-5% in that season.

Data on coverage rates for influenza vaccination of target groups is not available in Europe. However, we do know that the UK Department of Health recently increased its flu vaccination target for over 65's from 65% to 70%. We also know that healthcare workers are not routinely vaccinated for influenza in Europe.

In our model, we assume that European coverage rates of vaccination of key target groups are somewhat lower than in the US. Our assumed coverage of the older population in Europe is higher than in the US, because the European target group represents fewer patients (aged 65 years and older, rather than 50 years in the US). An upside to European vaccination rates would be a change to vaccination policy to cover those aged 50 years and older; however, we do not include this upside in our model.

We also expect the international market for flu vaccines (chiefly Eastern Europe, China, Taiwan, Mexico, Japan) to grow at the expected rate of GDP growth in these regions. We understand that the primary recipients of flu vaccines in these emerging regions are the affluent middle classes who can afford to pay nearly European prices for Western medicines.

■ Market Expansion from Launch of FluMist

As described above ("New Delivery Technology"), we expect that the impact of the FluMist launch will be to expand the flu vaccine market in the following ways:

1. **Increasing the awareness of flu vaccination** – we expect Wyeth and MedImmune to spend \$30 million on marketing for product launch in the 2003-4 flu season. The marketing message is likely to focus on the serious risks of influenza infection.
2. **Increasing the penetration in healthy workers** – previous experience in Europe with the nasally-administered Nasal flu (Berna Biotech; product now withdrawn) indicated that healthy individuals were willing to pay a significant price premium for convenient administration of the vaccine.
3. **Increasing the penetration in infants and young children** – we expect that parents would be more willing to vaccinate their children if a needle-free device were available (however, we do not expect FluMist approval in children <5 years until 2006, after more trials are completed successfully).

As a result of the above factors, we forecast that in 2003 in the US, penetration of key target groups will increase more so than in other years (an increase of 2% vs. 1%). We assume a similar impact in Europe in 2005, when we expect launch of the European formulation of FluMist (a liquid formulation, as opposed to the US frozen formulation).

We do not expect FluMist to have significant sales in the older population or in high-risk individuals, because its approved label will likely only include healthy individuals, aged 5-49 years, as recommended by the FDA Vaccines Panel in December 2002.

We expect that the launch of FluMist will significantly expand the market for vaccination of the healthy working population. In our model, we assume that FluMist will take some market share of vaccination of healthy workers and add about 5% to the coverage rate of this group in Europe and the US. Our end coverage rate is 14%, 7% of which we believe could still be served by injectable vaccines. Our expected peak sales of approximately 20 million doses of FluMist fits with Wyeth and MedImmune’s capacity plans for this product.

In 2006, following pediatric clinical studies, we believe that FluMist could be approved for use in children under five years. We expect that 10% of children would still receive injectable flu vaccines, with FluMist achieving an additional 7.5% market share by 2007. The increase in coverage of children from 3%-4% in 1999 to 18% by 2007 is consistent with the expected policy change by the US ACIP to recommend flu vaccination of all children aged 6-23 months, sometime in the next 1-3 years.

■ Pricing to Remain Relatively Flat

Following the price increases in the US and the UK in the 2000-1 flu season, we expect pricing to remain relatively stable in the future. We do not expect supply of vaccines to be limited in the next few years, so there is not likely to be a driver for higher prices of injectable vaccines.

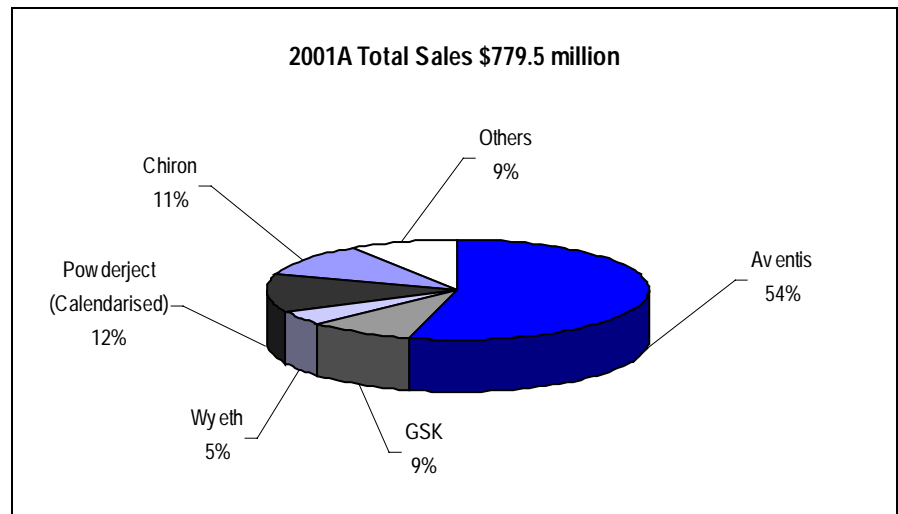
FluMist pricing will accelerate dollar value market growth

As a result of FluMist entry into the global influenza vaccine market, we expect the dollar market value to increase considerably from 2003E onwards. We expect FluMist to be launched at a price to the consumer of \$41. As described above, we expect certain groups, such as healthy workers, to be willing to pay this price premium. We understand that the FluMist production facility has fixed costs of \$50mn-\$60mn, plus variable costs of \$5 per dose. At peak capacity of 20 million doses, the cost of goods would be approximately \$7.50-\$8.00 per dose; hence the premium pricing is required to achieve reasonable margins.

■ Key Players in Global Flu Vaccines

Aventis dominates the global influenza vaccine market. In 2001, we estimate that Aventis had 54% US Dollar market share (see chart below).

Chart 5: 2001 Global Flu Vaccine US Dollar Market Share



Source: Company Data; Merrill Lynch estimates

Smaller players aided by being first to market

Other players GlaxoSmithKline, Chiron and PowderJect shared the majority of the rest of the 2001 market, with about 10%-15% market share each. Although much smaller companies than Aventis and GSK, both PowderJect and Chiron have made strong inroads into the US and European flu vaccine markets by being first to market with their new vaccines for the new flu season.

PowderJect has been first to ship new vaccine to the US market for the past three flu seasons, which has helped the company build up good relationships with customers. Likewise, Chiron has been first into the German market for the last two flu seasons. For these smaller companies, vaccines are a much bigger proportion of their overall business compared with the large pharmaceutical companies, so they focus more of their resource on their vaccine activities. For example, in December 2001, PowderJect was developing manufacturing processes for six possible strains, before the actual new strain was identified.

Smaller flu vaccine manufacturers with less than 10% market share include Solvay, Berna Biotech and Shire Pharmaceuticals. Wyeth captured 5% global market share in 2001 with its FluShield product, but has now withdrawn from the injectable vaccine market (see below). Wyeth will be marketing the MedImmune nasally administered FluMist product, which we expect to be launched in time for the US 2003-4 flu season.

■ **US Market – No Longer Capacity Constrained**

The FDA crack down on manufacturing led to flu vaccine shortages in 2000-1

In 1999, the FDA imposed new regulations on vaccine manufacturing. Many manufacturing processes had been in place for decades, and the FDA demanded that manufacturing systems be upgraded to reflect current good manufacturing practices. As a result, some companies were unable to supply flu vaccine for the 2000-1 flu season, because they had not completed the upgrades to their manufacturing systems in time. In addition, some companies like King (Park Dale) Pharmaceuticals withdrew from the flu vaccine market, because they did not wish to make the infrastructure investments.

As a result of the shortage in the 2000-1 flu season, there was a large increase in both volume and pricing in the 2001-2 flu season. The remaining US-approved manufacturers (Aventis, Wyeth and PowderJect) were able to supply 87 million doses to the US market for the 2001-2 flu season. We understand from CDC data that only about 90% of this supply (or 78 million doses) was actually used for vaccinations.

In 2002-3, supply was not a problem – and Wyeth found out the hard way

Following the vaccine shortages experienced in 2000-1, it had been commonly believed that the US market continued to be supply constrained. However, the current 2002-3 flu season demonstrated that this was not at all the case. CDC bulletins from November 2002 show that a total of 93 million doses of flu vaccine were produced, but that millions still had not been purchased.

In October 2002, Wyeth announced that it would have to write off flu vaccine stock worth \$35 million (approximately seven million doses), due to lack of sales. It appears that Aventis and PowderJect absorbed the majority of the contracts, because their flu vaccines were available to the US market much earlier than Wyeth's vaccine. The CDC October bulletin also stated that many vaccine orders had been cancelled after overbooking and multiple bookings made in the summer. It is possible that customers may have double booked contracts for Wyeth's vaccine, because they were uncertain that Wyeth could supply the vaccine. Since 1999, Wyeth had continued to be plagued by manufacturing issues for many of its vaccine products.

In November 2002, Wyeth announced that it would withdraw from the injectable flu vaccine market and instead concentrate on the 2003 launch of FluMist, its intra-nasally delivered flu vaccine. We believe that Wyeth will sell approximately 13 million doses of its FluShield flu vaccine in the current 2002-3 flu season.

Aventis and PowderJect should be able to make up the slack

With Wyeth out of the market, we estimate that there should be additional contracts available for at least 13 million flu vaccine doses, assuming no market growth. PowderJect had already planned to increase its global flu vaccine capacity from 27 million doses in 2002-3 to 35 million doses in 2003-4. We believe PowderJect supplied approximately 20 million doses to the US market in the 2002-3 flu season, so its US supply could be increased to 25-27 million. PowderJect has completed a significant proportion of a £15mn (\$23mn) capital investment program for its Speke UK facility, and we understand that the company is planning to further increase its Fluvirin production capacity beyond 35mn doses in the 2003-4 flu season.

Aventis has confirmed that it will increase its capacity for flu vaccines sold in the US, following withdrawal of Wyeth from the injectable flu vaccine market. For the current 2002-3 flu season, Aventis produced almost 44 million doses for the US market from its Swiftwater PA facility. We expect Aventis to be able to increase its US supply to 50-55 million flu vaccine doses for the 2003-4 flu season. Aventis had previously announced an \$80mn investment to increase flu vaccine fill and finish capacity at Swiftwater, and is evaluating even greater expansion over the next several years.

FluMist will expand the market rather than take market share

We believe that Wyeth/MedImmune's FluMist will mainly expand the market for flu vaccines to the healthy working population. At the premium price of \$40+ per dose and the logistical issues associated with frozen storage of product, we do not expect FluMist to take significant market share from the Aventis and PowderJect injectable vaccines in the key areas of older individuals and the high risk population.

■ **Winners Will be Those with a Marketing/Manufacturing Edge**

We expect those companies with strong established links with their customers to benefit in the long term. Aventis and GSK will likely continue to generate loyalty because they supply many important vaccines in addition to flu vaccines.

Market share maintained by close links with customers

We also believe that Powderject will be able to maintain market share if it continues to be first into the market with the season's new flu vaccine in the US. The reliability of supply generates its own loyal customer relationships in this biggest single market for flu vaccines. We believe a similar supply advantage in Germany could allow Chiron to retain market share as well.

As the flu vaccine market develops, we believe that market share will be taken by those products that can positively differentiate themselves from others. This should of course be the case for FluMist, but other injectable vaccines have positive product attributes. Berna Biotech, for example, has clinical data showing that their virosomal flu vaccine Inflexal V elicits greater antibody production (potentially predictive of protection from disease), and the company also possesses data (unpublished) that Inflexal V produces less pain on injection than standard injectable vaccines.

Needle-free Fluvirin launch possible in 2007

In September 2002, PowderJect completed a phase I volunteer study of its own needle-free flu vaccine, a powder formulation of Fluvirin delivered in the proprietary PowderJect device. The phase I study showed comparable immunogenicity to the injectable Fluvirin. We suspect that due to its different delivery characteristics, the needle-free Fluvirin may be considered a new vaccine by regulatory authorities, and require larger clinical studies prior to approval. As a result, we do not expect launch of needle-free Fluvirin before the 2007-8 flu season.

In our view, new market entrants that cannot differentiate themselves on marketing or manufacturing may struggle to take significant market share. Shire Pharmaceuticals already supplies flu vaccine to the Canadian market (about 2-3 million doses per year). The Canadian government has provided Shire with a grant to significantly expand its manufacturing capacity, so that Shire could supply the Canadian population with flu vaccine if there is an epidemic. We understand that

Shire will also be building excess capacity to allow it to enter the US vaccine market. Shire's product Fluviral is a split virus, which is not differentiated from other standard injectable influenza vaccines.

We believe that in order for Shire to make a significant impact on the US flu vaccine market (i.e. greater than 5% market share), it will need to have manufacturing processes at least as efficient as PowderJect's. In our view, the US market is not likely to be capacity constrained in the long term, and any market share will be won on time to market with the new season's flu vaccine.

■ Emerging Influenza Vaccine Manufacturers May Pose a Threat

In the long term, however, we believe that vaccines produced by new manufacturing methods may be a threat to existing injectable flu vaccines. Currently marketed flu vaccines are produced by an initial step of incubating the live virus in chicken eggs. For example, PowderJect has 300,000 pharmaceutical production quality chicken eggs delivered each day, when at full flu vaccine production capacity (Aventis probably has close to one million eggs delivered daily).

Both Baxter and Solvay are in advanced development of vaccines produced using more modern manufacturing methods, via cell culture. Baxter's Vero-cell (green monkey kidney) and Solvay's MDCK cell (Madine Darby canine kidney) culture systems are used to produce influenza virus antigens for use in their flu vaccines.

Cell culture-based vaccine production has been in development for many years, and has been plagued by a number of issues, including low yields and unstable cell lines. However, Baxter in particular has made recent strides with its Vero-cell culture system. In particular, the US government chose Baxter's proprietary Vero-cell system for the manufacture of new smallpox vaccine supplies (see Section 4).

Baxter's Vero-cell system is used to produce Influject, already available for sale in the Netherlands. We expect the first of two new Influject European manufacturing facilities to be on line for the 2004-5 flu season. Solvay has recently announced that it will invest in new manufacturing facilities for its MDCK cell culture-based flu vaccine. The MDCK vaccine is already approved in the Netherlands, and we expect Solvay to begin European supply from its new facilities late in the 2005-6 flu season. Aventis and Chiron are also working on cell culture processes for flu vaccines, but development is at a much earlier stage than Baxter and Solvay.

In terms of efficacy, the immunogenicity of these cell culture-derived vaccines appears to be similar to egg-derived vaccines. However, cell culture manufacturing methods may have several advantages over egg-based methods:

1. By removing the egg-processing bottleneck, cell culture manufacturing systems may have a start-up time advantage. For example, the entire production supply may be able to be manufactured in fewer runs.
2. Vaccine manufacturers are not reliant on egg supply, which could be an issue in a flu pandemic if there is a shortage of eggs.
3. Cell culture-derived flu vaccines could be promoted as having greater potential safety, as they do not have the same risk of contamination as egg-based flu vaccine manufacture.
4. Individuals with egg allergies can use cell culture-derived flu vaccines.

The first point may be the most important, if it turns out that cell culture systems may allow manufacturers to produce the final vaccine in less time than traditional egg-based systems. This could give the cell-culture companies a competitive edge in the race to be first to the market, which is particularly important for the US market. However, at this time, we understand that Baxter and Solvay have no concrete plans regarding supply to the US market.

Competitive threat from Baxter and Solvay

Baxter's Vero-cell flu vaccine is already launched in the Netherlands

If cell culture is faster than eggs, this could be an advantage in the US

Manufacturing risk is lower, these days

Safety issues remain a concern

Flu pills have not affected the vaccine market

Drug-like sales growth for flu vaccines

Risks to Influenza Vaccine Market Growth

Individual companies involved in the flu vaccine market face risks to growth mainly in the areas of manufacturing and safety concerns. Following the crack down on vaccine manufacturing in the US in 1999, most European-based companies also upgraded their manufacturing processes due to the expectation that the European authorities would also increase the stringency of their manufacturing regulations. As a result of flu vaccine manufacturing modernization, manufacturing risks have lessened. However, manufacture of flu vaccines still entails the manipulation of living organisms, so no system is risk-free.

Vaccines are administered to millions of healthy individuals, so any safety questions are not tolerated by the public or the regulators. In addition, it is very difficult to prove that a vaccine *does not* cause a particular side effect, without conducting a trial in thousands of individuals. Berna Biotech withdrew their Nasal flu vaccine from the European market in 2000, because of reports of a rare form of facial paralysis (Bell's Palsy) associated with vaccination. Berna was unable to disprove the link between Nasal flu and Bell's Palsy in a trial of 20,000 people (halted at 11,000).

Although manufacturing and safety issues can affect the growth of particular vaccine products, there are limited risks to overall growth of the flu vaccine market, in our view. The key risk is the development of flu treatment alternatives that replace flu vaccines.

■ Treatment Alternatives to Vaccines

Four prescription drugs are available for the prevention or treatment of influenza. These drugs have been available in the US and Europe for several years, and do not seem to have affected growth of the vaccines market. The reasons for the lack of success of these treatment alternatives may be related to their side-effects, the fact that flu symptoms still persist (although reduced in severity), and the narrow window required for starting effective therapy (patients need to obtain a prescription within 48 hours of onset of symptoms).

- **Tamiflu (oseltamivir phosphate)** – marketed by Roche, this neuraminidase inhibitor needs to be taken orally twice a day for five days for the treatment of influenza A or B.
- **Relenza (zanamivir)** – a neuraminidase inhibitor marketed by GlaxoSmithKline, this drug is inhaled twice per day for 5 days, for the treatment of influenza A or B.
- **Amantadine and rimantadine** – these orally-administered viral replication inhibitors can be used to prevent or treat influenza A only. Both of these drugs may produce undesirable side effects, such as light-headedness and difficulty concentrating.

In 2001, Tamiflu had sales of CHF 97mn (\$65mn) and Relenza had sales of £17mn (\$25mn). Unlike vaccines which are administered every year, sales of flu treatments fluctuate with the severity of the flu season. Both Relenza and Tamiflu are undergoing clinical trials to test their potential for prophylactic use.

Manufacturing Challenges

■ A New Jab Every Year

Flu vaccines are one of the few vaccine products that have drug-like sales growth, i.e. increasing annual sales. An individual needs a new vaccination every year to be protected against influenza, because the virus changes every flu season.

However, the downside of annual strain changes is that a new vaccine product needs to be developed every year, with the consequent revisions to manufacturing processes.

Refer to important disclosures at the end of this report.

■ A Timing and Manufacturing Efficiency Game

All flu vaccines have three strains (2A and 1B). Generally only one strain changes each year, which means that some aspects of the manufacturing process do not change. However, the exact composition of the vaccine is not defined usually until March every year, and vaccines need to start being shipped in July for the forthcoming flu season. If manufacturers waited for all three strains to be identified before starting the manufacturing cycle, then it would not leave nearly enough time to develop the amended manufacturing process for the new strain.

*A race to be first to market –
every year*

In practice, flu vaccine manufacturers start working up new strains much earlier, before the new strain has been officially identified. Global surveillance of emerging ‘flu strains occurs simultaneously with the ongoing flu season in the Northern hemisphere, i.e. from November to March. Observations are made regarding the emerging strains in the Southern hemisphere, and public information becomes available in December or January which narrows down the new strain to 2-3 candidates. Flu manufacturers will buy time by starting the manufacturing cycle early and adapting their manufacturing processes for all candidates, 2-3 months prior to final strain identification in March.

*On time delivery builds trust
and generates repeat contracts*

Timing is critical, particularly in the US market. Generally, the first manufacturer to ship flu vaccine to the US is the first to win the product contracts for the following year. In the US, almost all flu vaccine product is purchased by the end of November.. The European market is not characterized by such a deadline, and sales tend to continue into January, towards the end of the flu season.

In March, the recommended strains for the autumn flu season vaccine are officially announced by CDC (US Centers for Disease Control and Prevention), EMEA (European Agency for the Evaluation of Medicinal Products) and WHO (World Health Organization). All approved flu vaccines for that season will contain the officially designated strains. Occasionally, the recommendations from the three organizations differ slightly, and flu vaccine manufacturers who supply both the US and Europe may need to supply more than one flu vaccine product in one season.

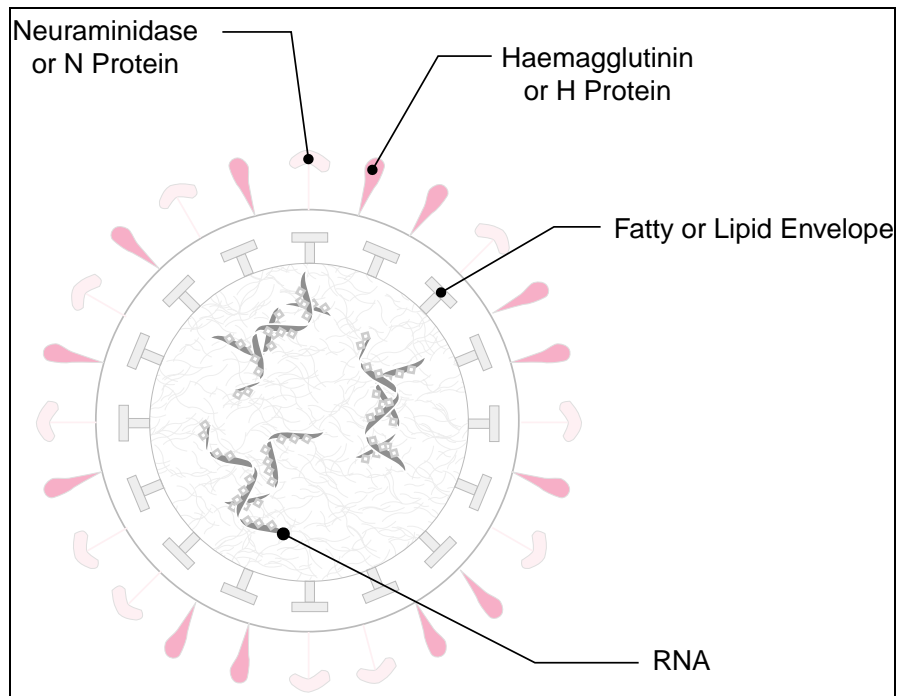
*A yearly trial in Europe,
test tubes in the US*

The flu vaccine approval process also differs between the US and Europe. Every year, European regulators require manufacturers to run a small clinical trial (200-250 people) to demonstrate immunogenicity of their new flu vaccine. The manufacturers need to show that the clinical trial participants develop antibodies (i.e. immunity) to the flu virus. In the US, flu vaccine manufacturers only need to conduct a test tube-based immune assay, without a clinical trial. The European and US testing usually occurs in June and May, respectively.

■ Get the Drift

There are three types of human influenza virus – A, B and C. Types B and C only infect humans, and type A can infect other animals as well. Influenza A viruses are most common and are the principal cause of widespread epidemics due to frequent changes in their surface proteins, called “antigenic drift”. Influenza B infections are often limited to localized outbreaks. Type C usually causes only mild disease, so is not used in vaccines.

Chart 6: Structure of the Influenza Virus



Source: National Foundation for Infectious Diseases; Merrill Lynch

Like all viruses, the influenza virus is a very simple – yet effective – organism. Its minimal genetic material (RNA) is encased in a protein core and surrounded by a lipid (fatty acid) membrane. On the surface of the lipid membrane are H (hemagglutinin) and N (neuraminidase) proteins that are used by the virus for docking and entering cells (see chart above).

The H and N proteins are the parts of the virus that are recognized by our immune system as foreign, and it is these proteins that are altered on the virus every year, rendering them unrecognizable as new strains when we are infected. The minor mutations that occur on the H and N proteins are referred to as “antigenic drift”.

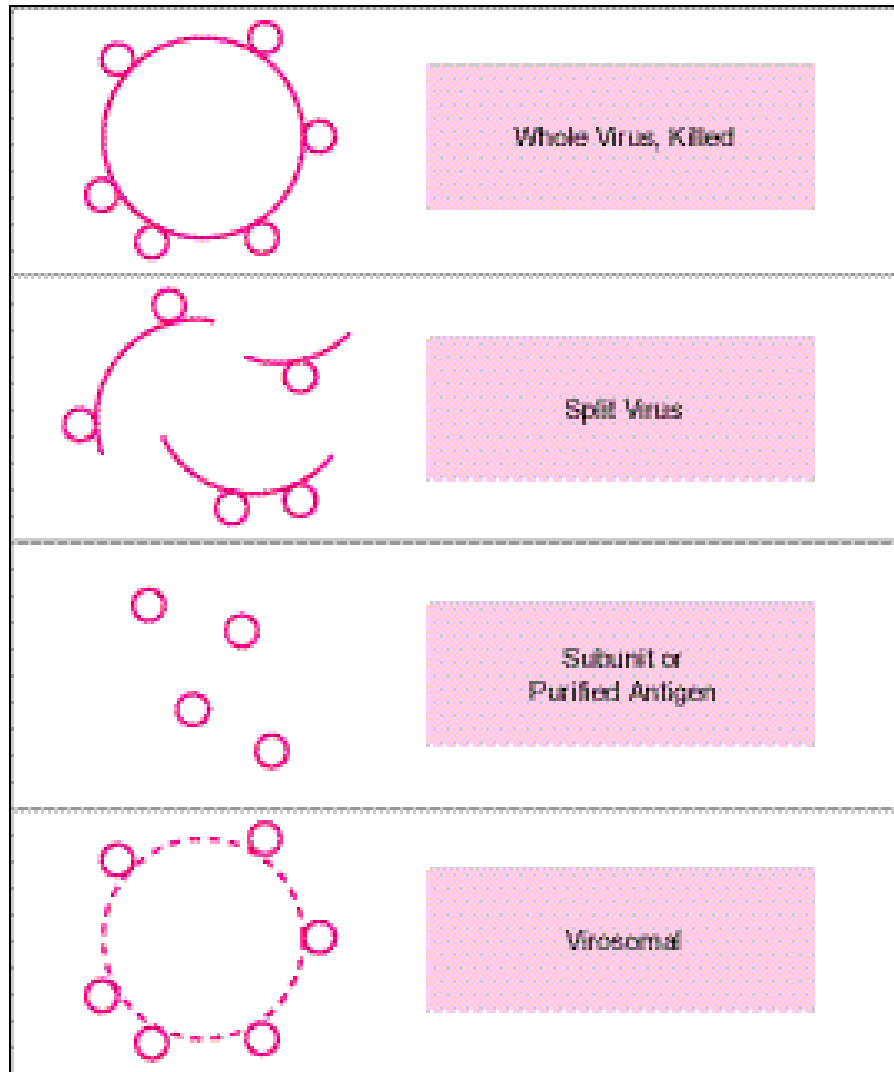
A major antigenic shift can result in a national epidemic or global epidemic (or “pandemic”). This is thought to be caused by genetic recombination of influenza type A viruses that have infected multiple species.

■ Effectiveness of Flu Vaccination

In general, the effectiveness of a flu vaccine depends on how well the chosen strains match the virus that is actually circulating during that particular flu season. Usually, flu vaccination can prevent influenza symptoms in 70%-90% of healthy young adults. However, the effectiveness of prevention may drop to 30%-40% in very frail, elderly people, because of their less robust immune system. Nonetheless, it has been shown that even if vaccinated individuals still contract influenza, the symptoms are less severe, and the risk of serious illness or death is significantly reduced.

■ Types of Influenza Vaccine

There are four different types of influenza vaccines available from manufacturers (see Chart). Whole virus vaccines are comprised of inactivated virus, and are rarely used now. Split virus vaccines are virus fragments, formed by disrupting virus particles with detergent. Subunit vaccines involve more processing, whereby the H and N surface protein antigens are purified away from other virus components. Virosomal vaccines are synthetic virus-like particles with embedded H and N surface protein antigens.

Chart 7: Types of Influenza Vaccine


Source: Merrill Lynch

All four types of vaccine are generally believed to be similarly effective in preventing influenza infection. A report by WHO found that the incidence of local reactions following vaccination (lasting 1-2 days) are more common in whole virus vaccines compared to subunit and split virus vaccines.

FluMist is old technology with a new twist

Whole virus vaccines are rarely used now, as they are considered old technology, apart from FluMist, which is a live cold-attenuated (weakened activity) influenza virus. The FluMist virus can replicate in the nasal mucosal membrane, but is rendered inactive elsewhere in the respiratory tract because of the warmer body temperature.

Head-to-head clinical trials of flu vaccines are not generally performed due to the associated costs of these potentially large studies (thousands of subjects would be required to compare actual levels of protection from infection). However, Berna Biotech has produced some positive clinical data comparing its virosomal vaccine to conventional vaccines. In a small study of 76 patients, Berna's Inflexal V virosomal vaccine was more immunogenic than conventional vaccines, as demonstrated by significant increases in antibody production and significantly greater levels of seroconversion. Unpublished evidence possessed by Berna also suggests that the virosomal vaccine causes less local pain than conventional vaccines.

Table 4: Global Flu Vaccine Model – Penetration Rates for Target Groups

	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
Flu Vaccinations (mn)									
US Flu Vaccinations	72	66	78	80	86	92	99	103	107
<i>% Growth</i>		(9%)	18%	3%	7%	7%	8%	4%	3%
Ex-US Flu Vaccinations	96	100	111	131	140	150	161	169	176
<i>% Growth</i>		4%	11%	18%	7%	7%	7%	5%	4%
Global Flu Vaccinations (mn)	168	166	189	211	226	242	260	272	283
<i>% Growth</i>		(1%)	14%	12%	7%	7%	8%	5%	4%
Older Population (000's)									
US Population >50 Yrs	75,358	76,472	77,602	78,746	79,904	81,077	82,264	83,774	85,303
<i>US Penetration %</i>	52%	49%	55%	56%	58%	59%	60%	61%	62%
Flu Vaccinations	39,186	37,089	42,681	44,098	46,345	47,835	49,358	51,102	52,888
Europe Population >65 Yrs	48,814	49,623	50,473	51,364	52,300	52,755	53,508	54,261	55,013
<i>Europe Penetration %</i>	59%	60%	63%	65%	66%	67%	69%	70%	71%
Flu Vaccinations	28,801	29,774	31,798	33,387	34,518	35,346	36,921	37,983	39,060
Older Population Market	124,172	126,095	128,075	130,111	132,204	133,832	135,772	138,035	140,316
<i>% Implied Growth Rate</i>		1.5%	1.6%	1.6%	1.6%	1.2%	1.4%	1.7%	1.7%
Flu Vaccinations (000's)	67,987	66,863	74,479	77,485	80,862	83,181	86,279	89,085	91,947
At Risk Population (000's)									
US Population at Risk	61,631	62,311	62,859	63,412	63,970	64,533	65,101	65,635	66,173
<i>US Penetration %</i>	21%	17%	23%	24%	26%	27%	28%	29%	30%
Flu Vaccinations	12,942	10,593	14,458	15,219	16,632	17,424	18,228	19,034	19,852
Europe Population at Risk	65,532	65,863	66,025	66,193	66,482	66,580	66,797	67,014	67,231
<i>Europe Penetration %</i>	18%	19%	21%	22%	23%	24%	26%	27%	28%
Flu Vaccinations	11,796	12,514	13,865	14,562	15,291	15,979	17,367	18,094	18,825
At Risk Population Market	127,163	128,174	128,884	129,605	130,452	131,113	131,898	132,649	133,404
<i>% Implied Growth Rate</i>		0.8%	0.6%	0.6%	0.7%	0.5%	0.6%	0.6%	0.6%
Flu Vaccinations (000's)	24,738	23,107	28,323	29,781	31,923	33,403	35,595	37,128	38,677
Healthcare Workers (000's)									
US Healthcare Workers	7,000	7,079	7,129	7,195	7,275	7,336	7,398	7,460	7,522
<i>US Penetration %</i>	42%	37%	46%	47%	48%	49%	49%	50%	50%
Flu Vaccinations	2,940	2,619	3,279	3,382	3,492	3,558	3,625	3,693	3,761
Europe Healthcare Workers	7,000	7,035	7,053	7,071	7,101	7,112	7,135	7,158	7,181
<i>Europe Penetration %</i>	36%	37%	40%	42%	43%	44%	46%	47%	48%
Flu Vaccinations	2,520	2,603	2,821	2,970	3,054	3,129	3,282	3,364	3,447
Healthcare Workers Market	14,000	14,114	14,181	14,266	14,376	14,448	14,533	14,618	14,704
<i>% Implied Growth Rate</i>		0.8%	0.5%	0.6%	0.8%	0.5%	0.6%	0.6%	0.6%
Flu Vaccinations (000's)	5,460	5,222	6,100	6,351	6,546	6,687	6,907	7,057	7,208
International (Ex-US, Ex-Eur)									
Flu Vaccinations (000's)	45,000	48,250	53,500	70,650	77,715	83,932	89,388	93,857	98,550
<i>% Growth</i>		7%	11%	32%	10%	8%	6%	5%	5%
Pediatric Population (000's)									
(Market Expansion)									
US Population <5 Yrs	14,399	14,162	14,115	14,066	14,015	13,963	13,908	13,962	14,017
<i>% Population <5 Yrs</i>	5.1%	5.0%	4.9%	4.9%	4.8%	4.8%	4.7%	4.7%	4.7%
Europe Population <5 Yrs	17,064	17,066	17,056	17,053	17,050	17,047	17,043	17,040	17,037
<i>% Growth of <5 Yrs</i>		0.0%	(0.1%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)	(0.0%)
Pediatrics Population Market	31,464	31,228	31,171	31,119	31,065	31,009	30,951	31,002	31,053
<i>% Implied Growth Rate</i>		(0.8%)	(0.2%)	(0.2%)	(0.2%)	(0.2%)	(0.2%)	0.2%	0.2%
Penetration by Inhaled Vaccine (Flumist)								4%	8%
Inhaled Vaccinations								1,238	2,325
Flu Vaccinations (000's)	1,101	1,093	1,184	1,245	1,553	1,861	2,476	4,340	5,434
<i>US and Europe Penetration %</i>	4%	4%	4%	4%	5%	6%	8%	14%	18%
Adult Working Population (000's)									
(Market Expansion)									
US Labor Force (000's)	140,436	142,016	143,015	144,350	145,950	147,176	148,412	149,658	150,916
Europe Labor Force (000's)	139,893	140,600	140,946	141,303	141,920	142,130	142,592	143,056	143,520
Adult Working Population (000's)	280,329	282,616	283,961	285,653	287,870	289,305	291,004	292,714	294,435
<i>% Implied Growth Rate</i>		0.8%	0.5%	0.6%	0.8%	0.5%	0.6%	0.6%	0.6%
Penetration by Inhaled Vaccine (Flumist)					2%	4%	6%	7%	7%
Inhaled Vaccinations					5,981	11,355	18,157	19,026	19,138
Flu Vaccinations (000's)	23,828	21,196	25,556	25,709	27,348	32,828	39,756	40,752	40,992
<i>US and Europe Penetration %</i>	9%	8%	9%	9%	10%	11%	14%	14%	14%

Source: Merrill Lynch estimates

Table 5: Global Flu Vaccine Model – Product Sales

	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
Sales Models									
Global Influenza Vaccine Market (\$mn)	464.2	507.1	779.5	961.6	1,255.9	1,508.7	1,806.3	1,933.3	2,017.7
% Growth		9%	54%	23%	31%	20%	20%	7%	4%
Fluzone/Vaxigrip (Aventis Pasteur)									
Flu Vaccinations (000's)	76,650	77,558	100,760	109,805	118,396	119,011	121,086	124,949	126,416
% Market Share	45.6%	46.8%	53.3%	52.0%	52.4%	49.2%	46.5%	45.9%	44.7%
Price of Vaccination	\$2.61	\$2.85	\$4.20	\$4.40	\$4.85	\$4.85	\$4.85	\$4.85	\$4.85
Fluzone/Vaxigrip Sales (EURmn)	188.0	240.0	473.0	493.0	585.4	588.4	598.7	617.7	625.0
Fluzone/Vaxigrip Sales (\$mn)	200.1	221.0	423.2	483.1	573.6	576.6	586.7	605.4	612.5
Fluarix (GSK)									
Flu Vaccinations (000's)	24,885	22,521	17,285	15,773	15,816	15,481	15,624	14,972	14,706
% Market Share	14.8%	13.6%	9.1%	7.5%	7.0%	6.4%	6.0%	5.5%	5.2%
Price of Vaccination	\$2.73	\$3.09	\$4.00	\$4.85	\$4.94	\$4.94	\$4.94	\$4.94	\$4.94
Fluarix Sales (€mn)	42.0	46.0	48.0	51.0	52.1	51.0	51.5	49.3	48.5
Fluarix Sales (\$mn)	67.9	69.6	69.1	76.5	78.2	76.5	77.2	74.0	72.7
Fluvirin (PowderJect)									
Flu Vaccinations (000's)	9,303	18,328	23,158	27,006	36,193	41,265	44,757	44,890	44,967
% Market Share	5.5%	11.1%	12.2%	12.8%	16.0%	17.1%	17.2%	16.5%	15.9%
Price of Vaccination	\$2.65	\$3.29	\$4.10	\$4.80	\$4.90	\$5.27	\$5.27	\$5.27	\$5.27
Fluvirin Sales (€mn with Mar YE)	55.0	14.0	40.6	66.7	87.4	118.9	145.3	157.2	157.7
Fluvirin Sales (\$mn)	24.6	60.2	94.9	129.6	177.2	217.4	235.8	236.5	236.9
Fluad & Begrivac (Chiron)									
Flu Vaccinations (000's)	20,968	20,594	19,318	19,309	20,335	20,319	20,311	20,144	20,362
% Market Share	12.5%	12.4%	10.2%	9.1%	9.0%	8.4%	7.8%	7.4%	7.2%
Price of Vaccination	\$3.10	\$3.40	\$4.40	\$5.50	\$5.44	\$5.44	\$5.44	\$5.44	\$5.44
Fluad & Begrivac Sales (\$mn)	65.0	70.0	85.0	106.2	110.6	110.5	110.5	109.6	110.7
Influvac (Solvay)									
Flu Vaccinations (000's)	16,928	17,080	16,984	19,855	20,561	20,319	18,228		
% Market Share	10.1%	10.3%	9.0%	9.4%	9.1%	8.4%	7.0%		
Price of Vaccination	\$2.65	\$2.75	\$2.95	\$3.10	\$3.09	\$3.09	\$3.09		
Influvac Sales (EURmn)	42.2	51.0	56.0	62.8	64.7	64.0	57.4		
Influvac Sales (\$mn)	44.9	47.0	50.1	61.5	63.4	62.7	56.2		
Inflexal V (Berna Biotech)									
Flu Vaccinations (000's)	2,358	2,163	2,141	3,908	4,971	5,080	5,208	5,444	5,656
% Market Share	1.4%	1.3%	1.1%	1.9%	2.2%	2.1%	2.0%	2.0%	2.0%
Price of Vaccination	\$4.23	\$4.79	\$6.20	\$6.16	\$5.93	\$5.69	\$5.44	\$5.44	\$5.44
Inflexal V Sales (CHFmn)	15.0	17.5	22.4	35.9	44.0	43.1	42.3	44.2	45.9
Inflexal V Sales (\$mn)	10.0	10.4	13.3	24.1	29.5	28.9	28.3	29.6	30.8
Fluviral (Shire Pharmaceuticals)									
Flu Vaccinations (000's)	2,747	2,697	2,292	2,323	3,457	4,596	7,421	7,758	7,777
% Market Share	1.6%	1.6%	1.2%	1.1%	1.5%	1.9%	2.9%	2.9%	2.8%
Price of Vaccination	\$2.18	\$2.47	\$3.20	\$3.88	\$3.96	\$3.96	\$4.55	\$4.55	\$4.53
Fluviral Sales (C\$mn)	9.0	10.0	11.0	13.5	20.5	27.3	50.6	52.9	52.9
Fluviral Sales (\$mn)	6.0	6.7	7.3	9.0	13.7	18.2	33.7	35.3	35.2

Source: Merrill Lynch estimates

Table 6: Global Flu Vaccine Model – Product Sales of Emerging Flu Vaccines

	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
Global Influenza Vaccine Market (\$mn)	464.2	507.1	779.5	961.6	1,255.9	1,508.7	1,806.3	1,933.3	2,017.7
% Growth		9%	54%	23%	31%	20%	20%	7%	4%
Influject (Baxter)									
Flu Vaccinations (000's)				158	169	3,870	7,552	16,333	21,776
% Market Share				0.1%	0.1%	1.6%	2.9%	6.0%	7.7%
Price of Vaccination				\$4.85	\$4.94	\$4.94	\$4.94	\$4.94	\$4.94
Influject Sales (\$mn)				0.8	0.8	19.1	37.3	80.8	107.7
FluMist (MedImmune & Wyeth)									
Flu Vaccinations (000's)					5,981	11,355	18,157	20,264	21,463
% Market Share					2.6%	4.7%	7.0%	7.4%	7.6%
Price of Vaccination (less 15% wholesalers discount)					\$34.85	\$34.85	\$34.85	\$34.85	\$34.85
FluMist Sales (\$mn)					208.4	395.7	632.8	706.2	748.0
MDCK Flu Vaccine (Solvay)									
Flu Vaccinations (000's)							1,302	16,333	18,383
% Market Share							0.5%	6.0%	6.5%
Price of Vaccination							\$3.09	\$3.09	\$3.09
Influvac Sales (EURmn)							4.1	51.4	57.9
MDCK Sales (\$mn)							4.0	50.4	56.7
Invivac Virosomal Vaccine (Solvay)									
Flu Vaccinations (000's)						484	781	1,089	1,273
% Market Share						0.2%	0.3%	0.4%	0.5%
Price of Vaccination						\$4.94	\$4.94	\$4.94	\$4.94
Influvac Sales (EURmn)						2.4	3.9	5.5	6.4
Invivac Sales (\$mn)						2.4	3.9	5.4	6.3

Source: Merrill Lynch estimates

Table 7: Global Flu Vaccine Model – Product Sales of Discontinued Flu Vaccines

	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
Global Influenza Vaccine Market (\$mn)	464.2	507.1	779.5	961.6	1,255.9	1,508.7	1,806.3	1,933.3	2,017.7
% Growth		9%	54%	23%	31%	20%	20%	7%	4%
FluShield (Wyeth)									
Flu Vaccinations (000's)	5,231	4,471	7,300	13,096					
% Market Share	3.1%	2.7%	3.9%	6.2%					
Price of Vaccination	\$3.25	\$4.25	\$5.00	\$5.40					
FluShield Sales (\$mn)	17.0	19.0	36.5	70.7					
Fluogen (King Pharma)									
Flu Vaccinations (000's)	8,831								
% Market Share	5.3%								
Price of Vaccination	\$3.25								
Other Flu Vaccines Sales (\$mn)	28.7								
Nasal Flu (Berna Biotech)									
Flu Vaccinations (000's)		90							
% Market Share		0.1%							
Price of Vaccination		\$36.71							
Nasal Flu Sales (CHFmn)		5.6							
Nasal Flu Sales (\$mn)		3.3							

Source: Merrill Lynch estimates

Table 8: Global Flu Vaccine Model – US Dollar Market Share

	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
Total Global Sales	464.2	507.1	779.5	961.6	1,255.9	1,508.7	1,806.3	1,933.3	2,017.7
Aventis	43%	44%	54%	50%	46%	38%	32%	31%	30%
GSK	15%	14%	9%	8%	6%	5%	4%	4%	4%
Wyeth/Medimmune	4%	4%	5%	7%	17%	26%	35%	37%	37%
PowderJect	5%	12%	12%	13%	14%	14%	13%	12%	12%
Chiron	14%	14%	11%	11%	9%	7%	6%	6%	5%
Solvay	10%	9%	6%	6%	5%	4%	4%	3%	3%
Berna Biotech	2%	3%	2%	3%	2%	2%	2%	2%	2%
Shire Pharmaceuticals	1%	1%	1%	1%	1%	1%	2%	2%	2%
Baxter	0%	0%	0%	0%	0%	1%	2%	4%	5%
Other	6%	0%	0%	0%	0%	0%	0%	0%	0%

Source: Merrill Lynch estimates

3. Travelers Vaccine Market

As more people travel to countries with endemic disease, demand for vaccinations will continue to increase. The largest markets for traveler's vaccines are dominated by large pharmaceutical companies, but smaller market opportunities also exist for smaller companies. In addition, the traveler's vaccine market presents a great marketing opportunity to increase awareness (and market size), because the majority of travelers do not take their recommended vaccinations.

Good Growth Expectations

The increase in travelers to areas of endemic disease has resulted in steady growth of the travelers vaccines market over the past few years. From World Tourism Organization (WTO) data for 2000, we estimate that 87 million people traveled from developed countries to regions with endemic diseases. In the long term, this number is expected to grow at approximately 5% annually. However, the increase in terrorism will likely continue to cause temporary global or regional declines in tourism and travel.

Continuing terrorism may temporarily impact 5-6% travel growth expectations

Table 13 shows that global tourism declined by almost 1%, following the terrorist attack in the US in September 2001. This decline followed several years of 4-7% annual growth in world travel. According to the World Tourism Organization, global tourism in 2002 recovered substantially from 2001 levels, and 5-6% annual growth is expected over the next several years. However, as a result of the terrorist attacks against Westerners in Bali in October 2002 and in Africa in November 2002, we also expect temporary reductions in travel to these regions in 2003.

There exists the risk of over-estimating travel vaccine market potential, due to two factors:

1. Travel vaccines are generally recommended, not mandatory, for travel to all regions of endemic disease (apart from some yellow fever regions), so there is a high percentage of the potential market that is never vaccinated;
2. Immunity lasts for a number of years with most travel vaccines, so if there is no "catch-up" phase, the market will consist only of new travellers to the region or the conversion of previously unvaccinated travellers; and
3. WTO tourism data reflects the number of travellers entering countries, but some travel to more than one destination in a single trip and return to destinations during the year, and these individuals would be counted as more than one person.

Travelers vaccines offer a big marketing opportunity

Nonetheless, the travel vaccines market represents a large marketing opportunity, in order to access the large unvaccinated population of travelers to regions of endemic disease by increasing awareness of the need for vaccination.

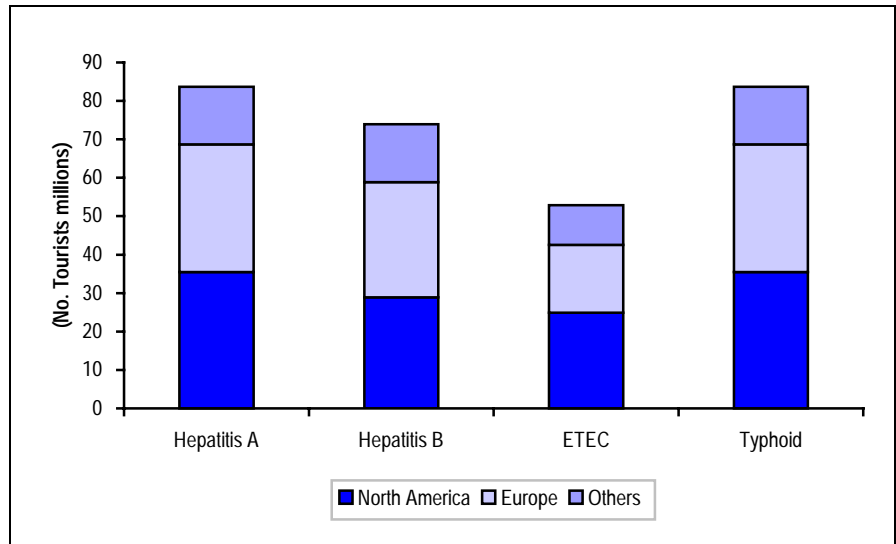
Room for Big and Small Players

Low hanging fruit picked early by big pharma

The biggest travel vaccine markets are for Hepatitis A and Typhoid, and the large pharmaceutical companies have dominant market share in these areas. Travel vaccines that target smaller markets, such as yellow fever and Japanese encephalitis are available for exploitation by smaller companies (see charts below). We suspect that these latter markets are too small for any big pharma competitors to actively defend their franchises from new entrants.

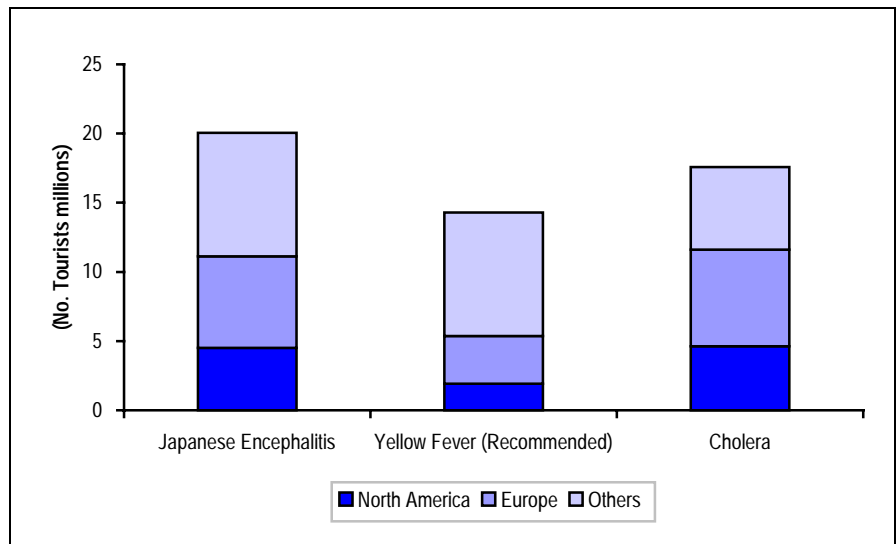
The market for traveler's diarrhea (ETEC vaccines) is potentially large in terms of numbers of vaccinations, and some smaller companies have development programs for ETEC vaccines. PowderJect already markets a traveler's diarrhea vaccine (Dukoral) in Scandinavia, and filed for European approval in 2002.

Chart 8: Numbers of Travelers to Major Endemic Disease Regions in 2001



Source: World Tourism Organization; Merrill Lynch estimates

Chart 9: Numbers of Travelers to Minor Endemic Disease Regions in 2001



Source: World Tourism Organization; Merrill Lynch estimates

■ **Hepatitis A**

Hepatitis A is highly contagious, and its flu-like symptoms, although not normally fatal, can lead to hospitalization. Our review of WTO data indicates that in 2001, almost 70 million people from North America and Europe traveled to Hep A endemic regions. GlaxoSmithKline markets Twinrix (HepA/HepB) to adult travelers, targeting those in Northern Europe who have not received Hep B vaccination as children.

■ **Typhoid Fever**

Typhoid fever is an acute systemic infection, caused by Salmonella typhi bacteria principally transmitted by contaminated food and water. If untreated, the illness is fatal in 12%-30% of cases. Typhoid fever can be treated with antibiotics, but there is growing antibiotic resistance. Typhoid is endemic in 153 countries, mainly in south and east Asia, Africa and South America.

Berna's Vivotif is a lot to swallow

Aventis and GSK market injectable typhoid vaccines, and Berna Biotech markets an oral typhoid vaccine. Although one would expect an oral vaccine to be more attractive than an injectable vaccine, the 3-dose five day regimen of Berna's Vivotif is unpopular, leaving it with a small share of the global typhoid vaccine market (2001 sales of approximately \$10mn).

■ **Japanese Encephalitis**

Japanese Encephalitis is a potentially fatal neurotropic viral infection, and the most common cause of viral encephalitis worldwide. JE is spread to humans by mosquitoes which transmit the virus from infected animals, mainly pigs. JE is endemic in parts of Australia and Asia, including Japan, Korea, Taiwan, China, India and Thailand.

Aventis markets the only approved JE vaccine in the US and Europe. The vaccine is comprised of killed virus, so its immunity is low (only lasts for about a year). Aventis' JE-VAX is mouse brain derived, administered in three doses one month apart, and suffers from side effects. Because of its unfavorable risk/reward profile, only those who travel to rural areas in JE endemic regions for one month or more are vaccinated. In the US, JE-VAX costs \$195 for three doses. The global market for JE vaccines is \$200mn per year, with 50% of sales in Japan (using a government developed vaccine that requires 6-8 doses).

5% of travelers currently take JE jabs

Using WTO data, we estimate that 11 million travelers from the US and Europe visited JE endemic regions in 2001. Extrapolating from the Aventis sales information about, we calculate that 5% of travelers to JE endemic regions were given JE-VAX.

Acambis is currently developing an alternative JE vaccine, which should begin phase III clinical trials by the end of 2003. Acambis' ChimeriVax-JE vaccine is derived from the live-attenuated 17D strain of the yellow fever virus, but it has been genetically engineered to confer immunity to JE virus. As ChimeriVax-JE has the yellow fever virus as its backbone, we expect a similar safety profile to established yellow fever vaccines (and therefore a better safety profile than Aventis' JE-VAX), and we also expect immunity from ChimeriVax-JE to last potentially for 10 years.

Acambis' JE vaccine may be a victim of its own success

We expect ChimeriVax-JE will be sold at a discount to JE-VAX, \$150 per dose compared to \$195 for three doses, to expand the market by increasing the uptake. In our view, pricing policy will be important to increase the penetration as many travelers would be unwilling to pay over \$100. The lower price, better single dose compliance and improved safety should enable ChimeriVax-JE to rapidly gain about 90% market share (of the 5% travelers to endemic regions who are vaccinated).

ChimeriVax-JE could have sales of \$120 million by 2010E

We assume that immunity will last for approximately 10 years (versus 1 year for JE-VAX) and that ChimeriVax-JE will be recommended by the WHO for most travelers visiting endemic regions (because of improved safety). As a result, we would expect penetration at 5% in the future to reflect a balance between (1) lower immunization rates due to longer immunity; and (2) higher immunization rates due to WHO recommendation. If half of all travelers are new, i.e. have not previously visited JE endemic regions, this is equivalent to penetration increasing from 5% to about 10% of travelers.

Our model below shows that we expect the Acambis JE vaccine to obtain sales of over \$120 million in 2010E, three years after launch in 2007E.

Table 9: JE Vaccine Sales Model

	2001A	2002E	2003E	2004E	2005E	2006E	2007E	2008E	2009E	2010E
Travellers to Recommended JE Regions (000's)	11,118	11,836	11,614	12,308	13,103	13,948	14,849	15,807	16,828	17,914
% Growth Rate	1.2%	6.5%	(1.9%)	6.0%	6.5%	6.5%	6.5%	6.5%	6.5%	6.5%
% Recommended Vaccinations Taken	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Number JE Vaccinations (000's)	556	592	581	615	655	697	742	790	841	896
JE-Vax (Aventis Pasteur)										
% Market Share of JE Vaccinations	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	85.0%	65.0%	25.0%	10.0%
JE-Vax Vaccinations (000's)	556	592	581	615	655	697	631	514	210	90
Price of Vaccine (3 doses)	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00	\$195.00
JE-Vax Sales (\$mn)	108.4	115.4	113.2	120.0	127.8	136.0	123.1	100.2	41.0	17.5
% Growth Rate	1.2%	6.5%	(1.9%)	6.0%	6.5%	6.5%	(9.5%)	(18.6%)	(59.1%)	(57.4%)
ChimeriVax-JE (Acambis)										
% Market Share of JE Vaccinations					0.0%	0.0%	15.0%	35.0%	75.0%	90.0%
ChimeriVax-JE Vaccinations (000's)					0	0	111	277	631	806
Price of Vaccine					\$150.00	\$150.00	\$150.00	\$150.00	\$150.00	\$150.00
ChimeriVax-JE Sales (\$mn)					0.0	0.0	16.7	41.5	94.7	120.9
% Growth Rate						n/a	n/a	148.4%	128.1%	27.7%
JE Market (\$mn)	108.4	115.4	113.2	120.0	127.8	136.0	139.8	141.7	135.7	138.4
% Growth Rate	1.2%	6.5%	(1.9%)	6.0%	6.5%	6.5%	2.8%	1.4%	(4.2%)	2.0%

Source: WTO data and Merrill Lynch estimates

Aventis' YF-VAX is not an ideal vaccine, but it does the job

US and European Arilvax sales could reach \$40mn in 2010E

■ **Yellow Fever**

Yellow Fever is caused by the Amaril virus, which is transmitted by the Aedes mosquito. Incidence has increased significantly in recent years, with up to 200,000 cases of yellow fever a year and about 30,000 deaths. Yellow Fever is endemic in tropical Africa and South America, plus several Caribbean islands (48 countries now reporting cases). Travelers to and inhabitants of endemic areas require vaccination. Yellow Fever is the only disease for which vaccine certification is mandatory before entry into certain countries, mainly in Central and West Africa.

The only Yellow Fever vaccine currently approved for sale in the US is Aventis' YF-VAX, a live attenuated vaccine that provides protection for 10 years to life. YF-VAX has been on the US market since 1975. It is not an optimal vaccine product, with only a one year shelf life and requiring storage on dry ice (-70 C). The average wholesaler price is \$57, but US servicemen obtain vaccinations for about \$21. We understand that the current US market is \$18mn-\$20mn, but this includes annual vaccination of about 300-400,000 military personnel each year.

In Europe, Aventis also markets the leading YF vaccine, called Stamaril. Compared to the US vaccine YF-VAX, Stamaril has a longer shelf life and does not need to be stored on dry ice. In the UK, the leading Yellow Fever vaccine is Arilvax, marketed by PowderJect. PowderJect relaunched Arilvax in the UK at £22 (\$33), a similar price to Stamaril, and we expect sales of £3.5mn (\$5.2mn) in CY2002.

PowderJect plans to launch Arilvax throughout Europe, starting mid-2003. Acambis is currently conducting a phase III clinical trial of Arilvax in the US, and we expect Arilvax to obtain US approval in 2007. Acambis has the rights to market Arilvax in the US for five years from launch. We expect Arilvax sales in the US and Europe to reach almost \$40mn by 2010E.

Based on WTO data, we have built a model for all travelers from the US and Europe to YF endemic regions, where vaccination is either mandatory or recommended (see Tables 10 and 11 below). For all models, we assume that all new travelers to mandatory YF regions are vaccinated.

Refer to important disclosures at the end of this report.

Extrapolating from the information on YF-VAX sales in the US, it appears that approximately 10% of US travelers to recommended YF regions are vaccinated each year, in addition to US military personnel. Using our estimates for PowderJect sales in the UK market, we conclude that 13% of all UK travelers to recommended YF regions are vaccinated, assuming that 30% of Arilvax sales are to UK military personnel.

In Europe, we expect Arilvax to obtain peak market share of 15% of travelers to recommended YF endemic regions, similar to the penetration achieved for Arilvax in the UK. This would equate to peak European sales of about £10mn (\$15mn), including sales in the UK, but not including sales to European military personnel. We do not expect revenues per dose to be as favorable as in the UK, however, as PJP will likely use distributors in Europe, rather than sell direct as in the UK.

In the US, we expect that Arilvax, when launched, will take market share from Aventis' YF-VAX, due to the longer shelf life (2 years) and more convenient storage (refrigeration) of Arilvax. In addition, once Acambis begins to actively market the importance of yellow fever vaccinations, we believe that Arilvax could increase the portion of travelers vaccinated from 10% to 15%. We do not expect penetration to rise above 15%, because (1) immunity lasts for 10 years, (2) some travelers will choose not to be vaccinated, and (3) a significant number of travelers return to previous destinations. We expect peak US sales of over \$20mn, equating to over 70% market share.

New mandatory YF vaccination regulations would be an upside

We have not included additional sales from vaccination of military personnel in the US and Europe, due to the likelihood of long term supply contracts already in place with Aventis. We understand that the US military contract for YF vaccines is not due to be renegotiated until 2005.

A significant upside to the Yellow Fever vaccine markets would be if countries such as the US required mandatory vaccination for US entrants returning from travel to YF endemic regions.

Table 10: US Yellow Fever Vaccine Sales Model

	2001A	2002E	2003E	2004E	2005E	2006E	2007E	2008E	2009E	2010E
Travellers to Mandatory YF Regions (000's)	70	74	70	74	78	83	87	92	97	102
% Growth Rate	(1.6%)	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
New Travellers Vaccinated (000's)	0	4	0	4	4	4	5	5	5	5
Travellers to Recommended YF Regions (000's)	1,921	1,999	2,056	2,140	2,227	2,318	2,413	2,511	2,614	2,721
% Growth Rate (* CAGR)	(4.8%)	4.1%	2.9%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%	4.1%
% Recommended Vaccinations Taken	10%	10%	10%	10%	11%	12%	14%	15%	15%	15%
Recommended YF Vaccinations (000's)	194	202	208	214	245	278	338	377	392	408
Number YF Vaccinations (000's)	194	206	208	218	249	282	342	381	397	413
Price of Vaccine for Civilians	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00	\$57.00
YF Civilian Market (\$mn)	11.1	11.7	11.8	12.4	14.2	16.1	19.5	21.7	22.6	23.6
Military Personnel (000's)	1,451	1,455	1,457	1,458	1,460	1,461	1,463	1,464	1,466	1,467
% Growth Rate	0.1%	0.3%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Military Personnel to YF Regions (000's)	334	335	335	335	336	336	336	337	337	337
% Personnel Vaccinated	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%	23.0%
Price of Vaccine for Military Personnel	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00	\$21.00
YF Military Personnel Market (\$mn)	7.0	7.0	7.0	7.0	7.1	7.1	7.1	7.1	7.1	7.1
Total YF Vaccinations (000's)	528	540	543	553	585	619	679	718	734	751
Total YF Vaccination Market (\$mn)	18.1	18.8	18.9	19.5	21.2	23.2	26.6	28.8	29.7	30.7
% Growth Rate	(3.4%)	3.8%	0.6%	3.1%	9.2%	9.0%	14.8%	8.4%	3.1%	3.2%
YF-Vax (Aventis Pasteur)										
% Recommended Travellers Vaccinated	10%	10%	10%	10%	7%	3%	2%	1%	1%	1%
% Market Share of Military Vaccinations	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
YF-Vax Sales (\$mn)	18.1	18.8	18.9	18.8	16.1	11.1	9.9	8.5	8.6	8.7
% Dollar Market Share of YF Vaccinations	100.0%	100.0%	100.0%	96.8%	75.7%	47.9%	37.1%	29.6%	28.9%	28.2%
% Growth Rate	(3.4%)	3.8%	0.6%	(0.2%)	(14.6%)	(31.1%)	(11.1%)	(13.5%)	0.8%	0.8%
Arilvax (Acambis)										
% Recommended Travellers Vaccinated				1%	4%	9%	12%	14%	14%	14%
% Market Share of Military Vaccinations				0%	0%	0%	0%	0%	0%	0%
Arilvax Sales (\$mn)				0.6	5.2	12.1	16.7	20.3	21.1	22.0
% Dollar Market Share of YF Vaccinations				3.2%	24.3%	52.1%	62.9%	70.4%	71.1%	71.8%
% Growth Rate				n/a	731.4%	133.9%	38.5%	21.3%	4.1%	4.1%

Source: WTO data and Merrill Lynch estimates

Table 11: UK and Europe Yellow Fever Vaccine Sales Models

	2001A	2002E	2003E	2004E	2005E	2006E	2007E	2008E	2009E	2010E
UK Sales Model										
Travellers to Mandatory YF Regions (000's)	38	40	38	40	42	45	47	50	53	56
% Growth Rate (* CAGR)	(3.0%)	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
New Travellers Vaccinated (000's)	0	2	0	2	2	2	2	3	3	3
Travellers to Recommended YF Regions (000's)	833	870	877	916	956	999	1,043	1,090	1,138	1,189
% Growth Rate (* CAGR)	(3.8%)	4.5%	0.8%	4.4%	4.4%	4.4%	4.4%	4.5%	4.5%	4.5%
% Recommended Vaccinations Taken		13%	13%	13%	13%	13%	13%	13%	13%	13%
Recommended YF Vaccinations (000's)		111	112	117	122	128	134	139	146	152
Number YF Vaccinations (000's)		113	112	119	125	130	136	142	148	155
Price of Vaccine for Civilians		£22.00	£22.00	£22.00	£22.00	£22.00	£22.00	£22.00	£22.00	£22.00
YF Civilian PJP Sales (£mn)		2.5	2.5	2.6	2.7	2.9	3.0	3.1	3.3	3.4
YF Military Personnel PJP Sales (£mn)		1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total YF Vaccination PJP Sales (£mn)		3.6	3.6	3.7	3.8	4.0	4.1	4.2	4.4	4.5
% Growth Rate		n/a	(0.8%)	4.4%	3.1%	3.2%	3.2%	3.3%	3.3%	3.4%
Europe Sales Model (incl. UK)										
Travellers to Mandatory YF Regions (000's)		291	276	291	307	324	342	361	381	402
% Growth Rate (* CAGR)		5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%	5.5%
New Travellers Vaccinated (000's)		15	0	15	16	17	18	19	20	21
Travellers to Recommended YF Regions (000's)		3,607	3,636	3,797	3,965	4,141	4,325	4,517	4,718	4,928
% Growth Rate (* CAGR)		4.4%	0.8%	4.4%	4.4%	4.4%	4.4%	4.4%	4.5%	4.5%
% Recommended Vaccinations Taken		6%	6%	9%	13%	15%	15%	15%	15%	15%
Recommended YF Vaccinations (000's)		198	200	342	515	621	649	678	708	739
Number YF Vaccinations (000's)		214	200	357	531	638	667	696	728	760
Price of Vaccine for Civilians		£12.50	£12.50	£12.50	£12.50	£12.50	£12.50	£12.50	£12.50	£12.50
YF Civilian PJP Sales (£mn)		2.7	2.5	4.5	6.6	8.0	8.3	8.7	9.1	9.5
YF Military Personnel PJP Sales (£mn)		1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total Arilvax PJP Sales (£mn)		3.8	3.6	5.6	7.7	9.1	9.4	9.8	10.2	10.6
% Growth Rate		n/a	(4.5%)	54.5%	39.2%	17.2%	3.9%	4.0%	4.0%	4.0%

Source: WTO data and Merrill Lynch estimates

■ Traveler's Diarrhea

ETEC (enterotoxigenic E. coli) is estimated to be the most frequent cause of traveler's diarrhea, usually transmitted by contaminated food or water. ETEC produce toxins that stimulate the intestine's lining to secrete excess fluid, resulting in the symptoms of diarrhea and abdominal cramping.

ETEC is endemic in 173 countries worldwide, and approximately 45 million people from North America and Europe annually travel to areas where contact with traveler's diarrhea is likely. About 30%-50% of visitors to Latin America, Africa and Asia suffer from diarrhea, compared to 10%-20% of travelers to the Mediterranean, eastern Europe and Russia.

ETEC is often resistant to antibiotics, and the only currently available vaccine is Dukoral, marketed by PowderJect in Sweden and Norway. Dukoral is an oral drinkable vaccine that protects against diarrhea caused by both cholera and ETEC. The ETEC immunization is actually conferred by cholera toxin subunit B (CTB), which has very similar antigenicity to ETEC. Aventis markets Dukoral in 13 countries outside Europe and the US, mostly in Latin America.

*No competition for Dukoral . . .
at the moment*

Dukoral is the only vaccine recommended and registered by WHO for vaccination of populations at risk of cholera epidemic. Berna Biotech markets another oral cholera vaccine Orochol, but it is not currently recommended by WHO. We understand that the WHO Global Task Force recently completed a retrospective

analysis of vaccination records and cholera cases in Micronesia, which showed an Orochol protective efficacy of 82%. We expect WHO to publish these data in the future and an Orochol recommendation could follow.

Dukoral sales in Sweden and Norway have been relatively stable for a few years at about £2.4mn (\$3.6mn) per year. Using WTO data, we can extrapolate from this sales figure and the £25 vaccination revenue that Dukoral is used by 15% of the 600,000 Swedish and Norwegian travelers to ETEC high risk regions every year. (In our model, we do not include the Eastern Mediterranean countries as a high risk regions).

\$50mn peak sales if Europeans mirror Nordic use of Dukoral

PowderJect filed for European approval of Dukoral in March 2002, and we expect the product to be approved by mid 2003. If we take the view that use of Dukoral in other European countries will be similar to use in Sweden and Norway, then we expect peak sales of about £34mn (\$50mn) would be achievable in major European countries (see our model in Table 12 below). In Europe, we would expect PowderJect to receive lower revenues per vaccination than in the Nordic countries, due to less favorable distributor relationships. PowderJect is currently in discussions with the FDA regarding a US filing for Dukoral. It is likely that PowderJect would need to generate US clinical data before it could achieve FDA approval, in our view.

Table 12: Europe ETEC Vaccine (Dukoral) Sales Model

	2001A	2002E	2003E	2004E	2005E	2006E	2007E	2008E	2009E	2010E
Europe Sales Model (incl. Scandinavia)										
Travellers to ETEC High Risk Regions (000's)	17,616	18,593	18,528	19,509	20,589	21,729	22,935	24,208	25,554	26,977
% Growth Rate (* CAGR)	1.7%	5.5%	(0.4%)	5.3%	5.5%	5.5%	5.5%	5.6%	5.6%	5.6%
% Travellers Taking Vaccines			1.2%	3.0%	5%	8%	10%	10%	10%	10%
Number ETEC Vaccinations (000's)			222	585	1,029	1,630	2,293	2,421	2,555	2,698
Price of Vaccine (Assuming 2 doses)			£12.50	£12.50	£12.50	£12.50	£12.50	£12.50	£12.50	£12.50
ETEC Market (£mn)			2.8	7.3	12.9	20.4	28.7	30.3	31.9	33.7
Norway and Sweden Sales Model										
Travellers to ETEC High Risk Regions (000's)	614	650	628	664	703	744	788	835	885	937
% Growth Rate (* CAGR)	1.7%	5.9%	(3.4%)	5.7%	5.9%	5.9%	5.9%	5.9%	5.9%	5.9%
% Travellers Taking Vaccines	15%	14%	15%	15%	15%	15%	15%	15%	15%	15%
Number ETEC Vaccinations (000's)	95	91	94	100	105	112	118	125	133	141
Price of Vaccine (Assuming 2 doses)	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00	£25.00
ETEC Market (£mn)	2.4	2.3	2.4	2.5	2.6	2.8	3.0	3.1	3.3	3.5

Source: WTO data and Merrill Lynch estimates

Table 13: Tourists from Developed Countries to Endemic Disease Regions

(No. Tourists 000's)	1990A	1995A	1998A	1999A	2000A	2001A	2002E	2003E	2004E	2005E	2006E	2007E
World	51,613	67,455	75,946	79,394	87,264	86,371	90,574	92,048	96,442	101,140	106,084	111,286
% Growth Rate (* CAGR)		5.5%*	4%*	4.5%	9.9%	(1.0%)	4.9%	1.6%	4.8%	4.9%	4.9%	4.9%
Africa	5,976	7,291	8,947	9,590	10,032	10,320	10,888	10,697	11,285	11,906	12,560	13,251
% Growth Rate (* CAGR)		4.1%*	7.1%*	7.2%	4.6%	2.9%	5.5%	(1.8%)	5.5%	5.5%	5.5%	5.5%
North Africa	3,792	3,290	3,907	4,250	4,542	4,786	5,049	5,150	5,433	5,732	6,047	6,380
% Growth Rate (* CAGR)		-2.8%*	5.9%*	8.8%	6.9%	5.4%	5.5%	2.0%	5.5%	5.5%	5.5%	5.5%
West Africa	448	634	798	870	926	897	946	899	948	1,001	1,056	1,114
% Growth Rate (* CAGR)		7.2%*	8%*	9.0%	6.4%	(3.1%)	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%
Central Africa	50	48	69	61	66	69	72	69	72	76	81	85
% Growth Rate (* CAGR)		-0.8%*	12.7%*	(11.9%)	7.9%	4.0%	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%
East Africa	1,218	1,917	2,361	2,530	2,627	2,655	2,801	2,661	2,807	2,962	3,125	3,296
% Growth Rate (* CAGR)		9.5%*	7.2%*	7.1%	3.8%	1.1%	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%
Southern Africa	469	1,402	1,811	1,879	1,872	1,914	2,019	1,918	2,024	2,135	2,252	2,376
% Growth Rate (* CAGR)		24.5%*	8.9%*	3.8%	(0.4%)	2.3%	5.5%	(5.0%)	5.5%	5.5%	5.5%	5.5%
Americas	25,127	30,098	33,586	34,274	36,260	34,297	35,634	37,024	38,468	39,968	41,527	43,146
% Growth Rate (* CAGR)		3.7%*	3.7%*	2.1%	5.8%	(5.4%)	3.9%	3.9%	3.9%	3.9%	3.9%	3.9%
North America	14,835	16,621	17,484	17,970	18,994	17,565	18,250	18,962	19,702	20,470	21,268	22,098
% Growth Rate (* CAGR)		2.3%*	1.7%*	2.8%	5.7%	(7.5%)	3.9%	3.9%	3.9%	3.9%	3.9%	3.9%
Caribbean	7,160	8,837	10,027	10,139	10,896	10,585	10,998	11,427	11,873	12,336	12,817	13,317
% Growth Rate (* CAGR)		4.3%*	4.3%*	1.1%	7.5%	(2.9%)	3.9%	3.9%	3.9%	3.9%	3.9%	3.9%
Central America	655	931	1,233	1,423	1,523	1,584	1,645	1,709	1,776	1,845	1,917	1,992
% Growth Rate (* CAGR)		7.3%*	9.8%*	15.5%	7.0%	4.0%	3.9%	3.9%	3.9%	3.9%	3.9%	3.9%
South America	2,478	3,708	4,842	4,742	4,847	4,562	4,740	4,925	5,117	5,317	5,524	5,740
% Growth Rate (* CAGR)		8.4%*	9.3%*	(2.1%)	2.2%	(5.9%)	3.9%	3.9%	3.9%	3.9%	3.9%	3.9%
East Asia and the Pacific	12,246	17,944	19,200	21,428	24,595	25,413	27,065	26,818	28,562	30,418	32,395	34,501
% Growth Rate (* CAGR)		7.9%*	2.3%*	11.6%	14.8%	3.3%	6.5%	(0.9%)	6.5%	6.5%	6.5%	6.5%
North-East Asia	5,446	8,574	9,868	10,744	12,448	12,768	13,598	14,482	15,423	16,426	17,493	18,630
% Growth Rate (* CAGR)		9.5%*	4.8%*	8.9%	15.9%	2.6%	6.5%	6.5%	6.5%	6.5%	6.5%	6.5%
South-East Asia	6,126	8,315	8,240	9,524	10,884	11,416	12,158	10,942	11,653	12,411	13,217	14,076
% Growth Rate (* CAGR)		6.3%*	-0.3%*	15.6%	14.3%	4.9%	6.5%	(10.0%)	6.5%	6.5%	6.5%	6.5%
Oceania	674	1,056	1,091	1,160	1,263	1,230	1,310	1,395	1,485	1,582	1,685	1,794
% Growth Rate (* CAGR)		9.4%*	1.1%*	6.3%	8.9%	(2.7%)	6.5%	6.5%	6.5%	6.5%	6.5%	6.5%
Europe	5,612	8,529	9,784	8,978	10,637	10,611	10,929	11,257	11,594	11,942	12,301	12,670
% Growth Rate (* CAGR)		8.7%*	4.7%*	(8.2%)	18.5%	(0.2%)	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
Central and Eastern Europe	1,921	2,888	3,286	3,200	3,370	3,330	3,430	3,533	3,639	3,748	3,860	3,976
% Growth Rate (* CAGR)		8.5%*	4.4%*	(2.6%)	5.3%	(1.2%)	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
Southern Europe	76	79	95	100	108	110	113	116	120	123	127	131
% Growth Rate (* CAGR)		0.7%*	6.4%*	5.3%	8.4%	1.2%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
East Mediterranean Europe	3,615	5,563	6,403	5,678	7,158	7,171	7,386	7,608	7,836	8,071	8,313	8,563
% Growth Rate (* CAGR)		9%*	4.8%*	(11.3%)	26.1%	0.2%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
Middle East	1,361	1,874	2,295	2,761	3,117	3,399	3,582	3,776	3,980	4,195	4,421	4,660
% Growth Rate (* CAGR)		6.6%*	7%*	20.3%	12.9%	9.1%	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%
South Asia	1,290	1,718	2,134	2,362	2,623	2,332	2,476	2,476	2,553	2,711	2,879	3,058
% Growth Rate (* CAGR)		5.9%*	7.5%*	10.7%	11.0%	(11.1%)	6.2%	0.0%	3.1%	6.2%	6.2%	6.2%

Source: WTO data and Merrill Lynch estimates

4. Other Vaccine Markets

The biggest single vaccine market today is pediatric vaccines, dominated by large pharmaceutical companies. Merck recently presented remarkable clinical data for a new HPV vaccine to prevent cervical cancer, and this could become a new blockbuster pediatric vaccine. Hepatitis vaccines are also a large market, but expiry of the hepatitis B patents in Europe will likely increase competition from developing world suppliers and drive down prices. Smallpox vaccines are grabbing attention as nations build stockpiles to vaccinate every citizen in the event of an outbreak.

Pediatric Vaccines – \$2.5 Billion Market and Growing

The market for pediatric vaccines was approximately \$2.5 billion in 2001, and is expected to grow 5%-7% per year.

Children up to the age of five years are routinely vaccinated against a multitude of childhood diseases. Vaccines for measles, mumps, rubella, diphtheria, tetanus, pertussis and polio represent approximately \$1.4bn in sales. In the US, all newborns are also vaccinated against hepatitis B, and in some states against hepatitis A. In addition, specialist pediatric vaccines are marketed for meningitis, pneumonia, chicken pox (varicella), and other diseases.

“Catch-up” then “top-up” sales growth pattern

New pediatric vaccine sales are generally characterized by a “catch-up” then “top-up” sales growth pattern. The first year or two following the launch of a new vaccine sees some of the highest sales revenues, as coverage is extended to all young children (the “catch-up” phase). In the following years, the sales of the vaccine grows only at the rate of the birth rate as newborns are vaccinated (the “top-up” phase).

The catch-up/top-up pattern is also seen in countries where a new universal immunization program is established for existing vaccines. For example, meningitis vaccines experienced large catch-up sales in the UK in particular, with a well-planned campaign to introduce this vaccine broadly in infants to 18 year olds. For example, in 2000 and 2001, Chiron’s Menjugate achieved annual sales of over \$100mn, primarily from introductions in the UK, Ireland and Canada. Current Menjugate annual sales are running at less than \$40mn worldwide, as only new infants are vaccinated now.

Big pharma dominates in pediatric vaccines

The pediatric vaccines market is dominated by large pharmaceutical companies, as the pattern of pediatric vaccine distribution fits well with their GP sales forces. Key players are Aventis, GlaxoSmithKline, Merck and Wyeth. The Vaccines and Diseases data base in Appendix I provides information on pediatric vaccines and combination vaccines that are marketed and in development.

■ Prevnar is a Pediatric Blockbuster

Prevnar, a pneumococcus vaccine launched by Wyeth in the US in 2000, provides an indication of the sales potential of specialist pediatric vaccines. Wyeth began developing Prevnar in the late 1980’s because pneumococcus was recognized as a serious cause of many diseases. In children, the pneumococcal pathogen is responsible for pulmonary (pneumonia), ENT (particularly acute otitis media), neuromeningeal (meningitis) or systemic (bacteremia and septicemia) infections.

\$800mn Prevnar sales in 2001, and supply cannot meet demand

In 2001, Prevnar had sales of \$798 million. At about \$60 per dose, Prevnar is double the price of other branded pediatric vaccines. The price premium is supported by the vaccine’s effectiveness. The conjugated vaccine was about 100% effective in prevention in large clinical studies, and it is now recognized by the CDC as an important vaccine. Wyeth is initiating a country-by-country launch throughout Europe.

However, Wyeth's supply is unable to meet demand for this vaccine. In September 2002, Wyeth announced that further manufacturing problems relating to the fill and finish part of the process would further limit supplies of Prevnar. Wyeth expects to have contract manufacturing validated for Prevnar by 3Q 2003. Due to the supply issues, we now expect Prevnar sales of \$584mn in 2002.

■ Growth Focused on Combination and Specialist Vaccines

Pharmaceutical companies acknowledge that the key to pediatric vaccine growth is reducing the number of different vaccinations by creating new combination vaccines. Pharma companies are even happy to cannibalize their own existing products by launching new combination vaccines or new forms of delivery that replace monovalent vaccines.

Key is to be "first with the most"

In combination vaccines, competitive advantage is gained by offering the most number of vaccines in a single injection. The market for combination vaccines is more developed in Europe than in the US, but products vary with regional differences in immunization programs. GSK's Pediarix, approved in late 2002, will be the first major combination vaccine in the US, covering Diphtheria, Tetanus, Pertussis, Polio (inactivated), and Hepatitis B. In the US, all newborns are routinely vaccinated for hepatitis B. However, some European countries (UK, Scandinavia, the Netherlands) do not include Hep B in their mandatory immunization programs.

Hexavac from Aventis is the biggest selling pediatric combination vaccine in Europe, with 2001 sales of EUR 450mn. Hexavac covers diphtheria, tetanus, pertussis, polio, Hib and Hep B. Aventis' next generation combination vaccine Pentacel (same as Hexavac, but no Hep B) has been slightly delayed in development, but they plan to file for FDA approval in 2003. A UK version Paediacell is currently in registration.

Another important means of differentiating pediatric vaccine products is the development of preservative-free vaccines. There have been some unsubstantiated concerns regarding thimerosal, a mercury-containing preservative that has been used in vaccines since the 1930's. In 1999, as a precautionary measure, the American Academy of Pediatrics agreed with vaccine manufacturers that newly licensed vaccines would contain no thimerosal or only trace amounts. Therefore, newer vaccines can be marketed as "preservative-free" compared to their older competitors.

Prevnar success spawns look-alikes

The clear marketability of Prevnar, coupled with Wyeth's inability to generate adequate supply, has resulted in a number of Prevnar copies in development. GSK plans to launch a similar product to Prevnar in Europe, with regulatory filing planned in 2004.

The Wyeth vaccine RotaShield, launched in 1998, had been on the same trajectory as Prevnar, but was withdrawn in 1999 due to serious (but rare) GI side effects. RotaShield was approved for the prevention of infection of rotavirus gastroenteritis in infants, but appeared to be associated with intussusception, a condition characterized by the folding of the intestine on itself.

The RotaShield recall left a gap in the market

Merck is developing a rotavirus vaccine ROTATEQ, which is in phase III clinical trials. Over 30,000 children have been enrolled in the 60,000 study, and there have been no cases of intussusception within a 42 day window post vaccination (with Rotashield, cases occurred within two weeks). Merck expects to file for approval of its rotavirus vaccine by 2006. GSK is also developing a rotavirus vaccine from a human strain of virus, as opposed to the animal strains that had been used in earlier products. GSK believe that their product could offer safety advantages and broader coverage.

Pharmaceutical companies we spoke to indicate that key growth areas in the next 5-15 years for specialist pediatric vaccines will be parainfluenza virus (Wyeth product entering phase I), RSV (respiratory syncytial virus causes high rate of pneumonia and mortality in very young children), bacterial meningitis,

streptococcus conjugate, and flu vaccines for young children. Companies see vaccinations for mild to serious disease becoming routine. Market share will be won by expanding valences (virus subtype coverage) and improving delivery.

Hepatitis – A Great Past, but Uncertain Future

Hep B patent expiration is set to depress European market value

Hepatitis is an inflammatory liver disease caused by the viruses Hepatitis A, B, C, D, E and G. Vaccines are available for Hepatitis A and B only. Hepatitis B sales have been declining globally, due to the tailing off of “catch-up” vaccination. Patents covering the hepatitis B vaccine started to expire in Europe in 2002, which will likely reduce the value of the global Hep B vaccine market further, as Europe opens up to lower priced competition from the developing world.

■ Hepatitis B

The World Health Organization estimates that there are about 350 million chronic carriers of hepatitis B virus (HBV) worldwide, resulting in about one million deaths per year. Highly endemic regions are tropical Africa, southeast Asia and China.

About 2%-5% adult HBV carriers develop chronic hepatitis, and about 20% of these develop cirrhosis and possibly hepatocarcinoma. In addition, 90% of newborns infected by their mothers become chronic HBV carriers. The primary means of HBV infection is sexual intercourse, intravenous drug use, and exposure to infected blood by transfusion or accidental contact.

In the US and most European countries, all newborns are vaccinated against Hepatitis B. Adult immunization is recommended for high-risk groups (healthcare workers, travelers to endemic regions, hemophiliacs, dialysis patients, organ transplant patients, infants born from carrier mothers, drug users, etc). In the UK, the Netherlands and some Scandinavian countries, there is no universal Hep B vaccination program for infants, and these regions represent potential growth areas.

A \$1+ billion market . . .

Hepatitis B monovalent vaccine was the largest single vaccine market in the world in 2001, with worldwide sales estimated at over \$1 billion. Aventis estimates that in 2001, European sales of Hep B monovalent vaccines were EUR25mn (\$274mn), North American sales EUR420mn (\$461mn) and rest of world EUR260mn (\$285mn). However, the Hep B vaccine market is in steady decline, due to declining “catch-up” immunization. No booster is required for long term immunity, and individuals who require vaccination have already been vaccinated. Therefore, the Hep B vaccine market will eventually grow at the rate of new births and new healthcare/high risk occupation workers (universal infant vaccination will also gradually whittle away this latter market over the next 20 years).

In the developing world, vaccination rates remain low, however. Therefore, there remains a significant market opportunity for Hep B vaccines in the developing world, although at much lower prices than in Europe and the US.

The first Hep B vaccines were produced from blood plasma of infected donors, because of the difficulty of reliably producing the Hep B virus in cell culture. The manufacturing challenge was solved by Chiron with a genetic engineering approach. Chiron introduced the genes for the Hep B virus antigens into standard production cells, and the first recombinant vaccine was approved in 1986. Merck licensed the Chiron intellectual property for its Recombivax HB vaccine, and GSK also licensed the Chiron technology for its Energix B vaccine. The Aventis-Merck JV sells Recombivax HB in Europe, and Aventis also uses the Merck Hep B antigens in its combination vaccines.

. . . unraveling as patents expire

Chiron’s hepatitis B vaccine patents started to expire in the first European countries in 2002, and expirations will continue in 2003 and 2004. The US patents (granted later than the European patents) will not expire until 2011 and 2012.

*Developing world Hep B
manufacturers will seek
European approval*

Patent expiry in Europe will allow generic competition to enter the Hep B vaccine market. Following the acquisition of Rhein Biotech, Berna Biotech has Hep B vaccine capacity of 150 million doses, produced by cost competitive yeast fermentation in a facility in South Korea. The Rhein facility currently supplies about 80 million doses of its Hepavax-Gene recombinant Hep B vaccine to Asian markets, as well as to developing markets via the supranational organization GAVI.

Shire Pharmaceuticals recently signed a collaboration with Berna to seek European approval of the Korean facility to register and market the Hepavax-Gene vaccine in Europe. We also understand that manufacturers in India have monovalent Hep B vaccine capacity of about 100 million doses. Wockardt of India is one of the companies likely to file for Hep B approval in Europe. The annual market for Hep B vaccine is about 35 million in India alone, and it is driven by five different players.

■ **Hepatitis A**

Hepatitis A is a highly contagious disease, transmitted person-to-person via the fecal-oral route. Hepatitis A is the least dangerous form of hepatitis because it is rarely fatal and does not lead to chronic inflammation of the liver. However, recovery from the flu-like symptoms of hepatitis A can take up to six months and may require hospitalization.

Incidence of hepatitis A is closely related to socioeconomic status. Endemic areas are Latin America, Asia and Eastern Europe. Risk groups include travelers, medical personnel, populations in endemic regions, food handlers, active male homosexuals, intravenous drug users and military personnel.

Hep A immunization is currently reserved for high-risk groups, and is also required for infants in certain US regions that border Mexico. For travelers, a booster is required after the trip to give three years of immunity.

*A \$400mn market dominated by
big pharma*

The Hepatitis A vaccine market is estimated to be worth about \$400 million. GlaxoSmithKline, Merck and Aventis dominate. GSK's Havrix was the first to reach the market, and has been used to immunize over a million individuals to date. Merck's Vaqta has been successfully targeted at the infant market in the US (it is preservative-free), but has been used to immunize less than 50,000 individuals since launch. Berna Biotech markets the virosomal vaccine Epaxal, but recent manufacturing issues have hampered European sales (approximately \$3mn in 2001).

GSK also markets a combination Hep A/Hep B vaccine Twinrix, which is mainly sold to travelers. Since its launch, Twinrix has cannibalized much of GSK's Havrix sales. The Twinrix combination vaccine is patented until 2008 in Europe, so it will be protected from generic Hep A/Hep B copies following expiration of the European Hep B vaccine patents. GSK and Aventis also market a combination of Hep A/Typhoid vaccine for travelers.

Bioterrorism

Following the terrorist events in the US in September 2001 and the anthrax scare in October 2001, there is heightened concern that terrorist organizations may use biological agents as weapons of bioterrorism. Many candidate bioterrorist agents (such as anthrax) can be treated with existing antibiotics or antiviral therapy (see below). However, most concern has focussed on smallpox, a deadly disease that can only be prevented by vaccination.

■ **Smallpox Background**

Smallpox is caused by the variola major virus that emerged in humans thousands of years ago. Smallpox is highly contagious, transmitted person to person primarily by expelled aerosolized saliva droplets, but also by skin contact.

Smallpox eradication ended routine vaccination in 1980

Up to 30% of those infected with smallpox die. In the last century, there were 300 million deaths from Smallpox infection. Following a global vaccination campaign, WHO declared the smallpox virus eradicated in 1980. The last US case of smallpox occurred in 1949. The last naturally occurring case in the world was in Somalia in 1977.

After the disease was eliminated, routine vaccination against smallpox was discontinued. As smallpox vaccination is believed to last no more than 20 years, the world's population is now not adequately protected from new outbreaks. Following the increased terrorist activity in 2001 and 2002, many governments are taking increased precautions to be prepared for a potential smallpox outbreak.

■ US Vaccine Stockpiles Accelerated Post-Sept 11th

The US government originally began stockpiling smallpox vaccine with a contract awarded to the UK company Acambis in September 2000. The \$343mn contract was to develop a new smallpox vaccine, and to create and maintain a stockpile of 40 million doses over 20 years, with first deliveries to the CDC planned in mid-2004. (The contract value is actually worth \$95mn; the \$343mn headline value was purely an indicative number for US Congress budgeting purposes, as the actual cost had not yet been determined.)

The new ACAM1000 vaccine is based on the same vaccinia virus strain ("New York City Board of Health", NYCBOH) that was licensed in the US and used for routine immunization against smallpox prior to global eradication. Vaccinia is from the same orthopox virus family as variola virus, and induces an immune reaction that protects against the more virulent variola virus that causes smallpox. ACAM1000 is manufactured using human fibroblast cell culture (MRC5 cell line).

The US has ordered 209mn doses from Acambis-Baxter

Following the terrorist events in the US, the US Government decided to create a smallpox vaccine stockpile large enough to provide a dose for every US citizen. In October 2001, the original contract with Acambis was expanded to 54 million doses and accelerated, requiring delivery by the end of 2002. In addition, the US government invited tenders for a new, much larger, contract to manufacture sufficient supplies of smallpox vaccine for the entire population.

In November 2001, the US government awarded the new \$428mn smallpox contract to Acambis in partnership with Baxter. This second contract was to supply 155 million doses by the end of 2002, expanding the total number of doses to be supplied by Acambis to 209 million.

The second contract is for delivery of a new vaccine ACAM2000, which is produced using Baxter's proprietary Vero-cell culture system. The expectation is that smallpox vaccine from cell culture will have fewer potential contaminants than the older smallpox vaccines, which were made from vesicle fluid of calves deliberately infected with vaccinia virus. Acambis is the prime contractor whilst Baxter assists with the bulk manufacture.

The ACAM2000 is being tested in clinical trials for safety and efficacy, compared to ACAM1000 and the calf-lymph vaccine Dryvax (see below). Clinical efficacy is determined by "take" or pock formation, plus production of neutralizing antibodies. Submission for FDA approval is expected in mid-2003.

The US already has a stockpile of 100mn doses of old vaccines – enough to vaccinate over 400 million people

While the US is waiting for delivery of the Acambis-Baxter vaccines, there exist adequate supplies of older vaccines for ring vaccination or even mass vaccination in the event of a deliberate release of smallpox. The US still holds 15 million doses of Dryvax, a calf-lymph vaccine made by Wyeth in the 1970's. In recent studies, Dryvax was shown to be potent at a 1/5 dilution, which means vaccine is available for vaccinating 75 million people. The US paid \$12mn to Aventis for 85 million doses of a similar calf-lymph vaccine manufactured in the 1950's, which in recent testing was shown to be fully potent, even at 1/5 or 1/10 dilutions. Therefore, the Aventis vaccine alone could be used to immunize over 400 million people in a bioterrorist emergency.

In December 2002, the US government announced that it would undertake a limited pre-event smallpox vaccination program. Under these proposals, designated “Smallpox Health Care Teams” and certain military personnel would be vaccinated as a precautionary measure prior to any smallpox epidemic. The US government expects to vaccinate up to 5-6 million people under this program, using undiluted supplies of Dryvax. This figure includes 500,000 military personnel and 400,000-500,000 healthcare workers who are together designated “first response” teams. The second group of about five million people will include remaining healthcare workers and traditional first responders. The US government also stated that it would make available smallpox vaccine to any citizen who insisted on being vaccinated.

***The US currently favors “ring”
vaccination . . .***

The current US emergency smallpox vaccination policy is to give priority to those who have been in contact with the patient since onset of fever, plus all household members of the contacts. This “ring vaccination” strategy provides a buffer zone of immunity to prevent further spread of smallpox infection.

***. . . because mass vaccination
could overwhelm the health
care system***

Mass vaccination of the population prior to a smallpox outbreak is not favored by the US government, due to safety concerns regarding side effects of smallpox vaccination. The CDC states that judging from past vaccination experience, 1,000 out of 1 million people vaccinated with smallpox vaccine today would be expected to suffer side-effects that required medical attention. Up to 50 people out of every million vaccinated could suffer life-threatening side-effects that would require hospitalization, and between one and two people out of one million would be expected to die as a consequence of vaccination. If 280 million Americans are vaccinated, 14,000 could be hospitalized, with over 400 deaths.

***The US has enough doses for
post-outbreak mass-vaccination***

New vaccines like the Acambis-Baxter ACAM2000 could only be shown to be safer than the older vaccines if trials were conducted in tens of thousands of volunteers. Therefore, we do not expect the availability of newer vaccines to be used for pre-emptive mass vaccination unless large trials are conducted that show acceptable safety levels.

However, if there is a smallpox epidemic that is not contained by ring vaccination, we would expect the US government to perform mass vaccination, as the deaths from smallpox would be substantially greater than deaths from vaccination. Up to 30% of the US population would (84 million) would be expected to die if all were infected, vs. 1-2 out of 1 million deaths (400) from vaccine side effects.

Therefore, we would expect the US to maintain enough smallpox vaccine supplies to vaccinate every individual, as a precautionary measure. Once the Acambis-Baxter contract for 209 million doses is fulfilled in 2003, the US government will have more than enough doses to vaccinate every American against smallpox (including 400+ million doses of calf-lymph vaccine). We expect that over the next several years, the US government will continue to contract supplies of smallpox vaccine from Acambis under an existing maintenance contract, so that the cell-culture vaccine eventually replaces stocks of the older calf-lymph vaccine.

***VaxGen may not have the right
strain to compete in the US***

In December 2002, the US company VaxGen announced that it had licensed US development and distribution rights to the LC16-Kaketsuken smallpox vaccine, a cold-attenuated (weakened) strain derived from the Lister vaccinia strain. This particular vaccine was licensed in Japan in 1980, and it demonstrated a much better safety profile than other smallpox vaccines when administered to 50,000 Japanese children <2 years old. VaxGen plans to start clinical trials of the LC16-Kaketsuken vaccine in early 2003. Although the LC16 vaccine may be shown to be potentially safer, we believe it is unlikely that the US government would choose to contract supply with a different strain of vaccine than its current supplies of NYCBOH strain vaccine.

■ Potential Upside from Stockpiling by Other Nations

Most countries outside of the US do not currently possess smallpox vaccine stockpiles sufficient to vaccinate every individual. We expect that other governments will use the same strategy as the US, i.e. (1) conduct pre-event vaccination of key “first response” health care workers, and (2) build up a stockpile of enough doses to vaccinate every individual in the event that mass vaccination is ever required.

Most European nations previously used smallpox vaccines based on the Lister strain of vaccinia virus, so it is likely that only companies that can supply Lister-based vaccines will win new contracts, in our view.

The UK is one of the first to follow suit

The UK previously purchased what we estimate to be 20 million doses of smallpox vaccine from PowderJect (Bavarian Nordic Lister strain of vaccinia vaccine). In December 2002, the UK outlined a plan for pre-event vaccination of key personnel, followed by a “ring” vaccination strategy. Simultaneously, the UK announced that it had put out for tender a contract to provide what we estimate to be 40 million more doses of smallpox vaccine (which would cover the entire UK population in the event of mass vaccination).

Some other European countries have already purchased supplies of smallpox vaccine, but none of these have enough to vaccinate every member of their population. Recently, Austria and Canada have indicated that they are seeking supplies of smallpox vaccine.

PowderJect is well-placed to provide vaccines

In our view, the only companies who will be able to supply smallpox vaccine to these European countries are PowderJect, Berna Biotech and Bavarian Nordic. Acambis’ ACAM2000 vaccine is derived from the NYCBOH strain, not the Lister strain favored by European nations.

Berna Biotech has supplied CHF170mn (\$110mn; we estimate approximately 50 million doses) worth of smallpox vaccine to European countries. We believe Berna has approximately 30mn doses left of its original smallpox vaccine supply. We understand that Berna does not have any further production capacity. However, both PowderJect and Bavarian Nordic have the capability to manufacture and supply the Bavarian Nordic vaccine to European countries.

A stockpile for all Europeans would need 100-200mn more doses or \$300mn in revenues

If all European countries follow the lead of the US and the UK, then we believe there could be an additional demand for 100-200 million doses or about \$300 million in potential revenues.

■ Other Bioterrorism Targets

Many biological agents that could be used as weapons of bioterrorism can be effectively treated using current available medicines. As reported in a July 2002 study by the EMEA (CPMP/4048/01), available antibiotics such as Ciprofloxacin and doxycycline can be used to effectively treat infections of Anthrax, plague (*Yersinia pestis*), Tularemia, Brucellosis, Q Fever, Glanders & Melioidosis, Psittacosis, and Epidemic Typhus. Some viral hemorrhagic fevers, such as Lassa Fever, can be treated with anti-viral drugs such as Ribavirin.

Many other potential bioterrorist agents can be treated with existing drugs

Due to developing antibiotic resistance, diseases such as Shigellosis, Salmonellosis and TB may be less effective with available antibiotics. No current therapy exists for treatment of viral hemorrhagic fever from infections of Marburg and Ebola viruses. The US National Institutes of Health are currently providing funding for the Dutch biotechnology company Crucell to develop vaccines for Ebola, Marburg and Lassa viruses.

AIDS Vaccines – There's Still Hope

AIDS (acquired immunodeficiency syndrome) is caused by infection with human immunodeficiency virus (HIV). This virus is passed from one person to another through blood-to-blood and sexual contact. According to UNAIDS and WHO, the number of people infected with HIV in the world today has risen to 42 million, up from 40 million at end 2001. In 2002, there were 3.1 million deaths from AIDS world wide.

The majority of AIDS cases are outside of the developed world. In the US, the cumulative number of AIDS cases reported to CDC is 816,149. The CDC reports a total of 467,910 deaths from AIDS in the US. In Europe, there were approximately 500,000 individuals infected with HIV at the end of 2001, according to UNAIDS data.

Deaths from HIV have decreased in the developed countries due to treatment with anti-retroviral drugs that control replication of the virus. These drugs are now being made available to patients in developing countries as well.

Ever since the 1983 identification of HIV as the cause of AIDS, there has been a search for an effective prophylactic HIV vaccine. However, due to the rapid mutability of the HIV surface proteins, an effective vaccine has been elusive.

One promising vaccine candidate is VaxGen's AIDSVAX, currently in phase III clinical studies. AIDSVAX contains copies of the HIV surface protein gp120. VaxGen is running two clinical studies: (1) 5,400 individuals in North America and the Netherlands, targeting HIV strains prevalent in North America and Western Europe; (2) 2,500 individuals in Thailand, targeting HIV strains prevalent in Southeast Asia and the Pacific Rim. Data from the North American study should be available in 1H 2003.

Merck also has two HIV vaccine candidates in a total of 10 phase I clinical trials. About 1,300 uninfected and HIV-infected volunteers are taking part in the studies.

If the HIV vaccine studies are successful, the market for this vaccine could be substantial, as it would likely be provided as compulsory vaccination to young children.

First phase III data for HIV vaccine expected 1H 03

West Nile Virus – An Emerging Disease

The West Nile Virus causes encephalitis or meningitis (inflammation of the brain or spinal cord). WNV replicates in birds and is transmitted by mosquitoes from birds to humans. Only about 20% of those infected develop symptoms, and most infections are mild. Less than 1% develop severe disease, and about 7% of people hospitalized with WNV infection die from it. The segments of the population considered most at risk are young children and those aged 55+ years.

WNV is endemic in the Middle East, Africa and parts of Europe. WNV was first identified in the US in 1999 (62 cases of severe disease were reported that year). Since mosquitoes and migratory birds carry the virus, it has continued to spread throughout the US. At the beginning of December 2002, the CDC reported a total of 3,775 cases in 39 states. Of these US cases reported since 1999, there have been 216 deaths. The 2002 outbreak was more extensive than in 1999, when the virus first appeared in New York City.

In the US, there are campaigns to spray pesticides to control mosquito populations, but historically, this approach has had limited impact in controlling mosquito populations.

WNV has caused 216 deaths in the US so far

***WNV vaccine development
could be accelerated by the US
government***

Acambis has a WNV vaccine in early development. Phase I clinical trials are expected to begin in 1H 2003. The vaccine candidate ChimeriVax-West Nile is derived from the live attenuated 17D strain of the yellow fever virus, but it has been genetically engineered to confer immunity to WNV while possessing a yellow fever virus backbone. This vaccine was developed with the aid of funding from the US National Institutes of Health.

If the disease continues to spread significantly in the US and is considered to be a threat, there may develop a need for a WNV vaccine for compulsory vaccination in certain states or nation-wide. It is possible that, similar to the US small pox stock-piling efforts, the US government may seek to accelerate clinical development of a WNV vaccine.

Human Papilloma Virus – Blockbuster Potential

Human papillomavirus (HPV) is the most common sexually transmitted infection. The outward manifestation of HPV is genital warts, but most of those infected do not have symptoms. It is estimated that HPV infection is present in 20% of asymptomatic sexually active women.

Cervical cancer is directly linked to HPV infection. It is estimated that 10% of all women infected with HPV will develop precancerous changes in their cervical tissue (dysplasia). Of these, about 8% will develop early cancer in the outer layers of the cervix (cervical intraepithelial neoplasia or CIN), and 2% will develop invasive cancer unless the precancerous lesions are detected (by pap smear) and treated. Before pap smear testing became routine, cervical cancer was the number one cause of cancer death in women.

A 1999 study by Groopman monitored over 600 female university students who were tested for HPV every six months. During the three year study, new HPV infections occurred in more than 40% of the women. Most infections lasted about eight months and then subsided. After two years, however, about 10% of the women still carried active virus. In this study the persistent infections were mostly caused by the cancer-linked HPV subtypes, i.e. HPV-16.

***Merck's HPV vaccine could
help wipe out cervical cancer***

In November 2002, *The New England Journal of Medicine* published remarkable clinical data on a novel HPV vaccine, developed by Merck and CSL of Australia. In the phase II double-blind placebo-controlled study, 2,392 women aged 16-23 were vaccinated with an HPV-16 L1 virus-like-particle monovalent vaccine. The women were tested for HPV infection every six months, and they were followed on average for about 18 months. In this study, Merck's HPV vaccine showed 100% efficacy. In the vaccinated women, the incidence of HPV infection was 0 per 100 woman-years at risk versus 3.8 in the placebo group ($p < 0.001$). In addition, all nine cases of CIN occurred in the placebo group.

In 1Q 2002, Merck began enrolling women in a phase III study that will test the quadrivalent vaccine that Merck intends to market.

\$840mn sales expected by 2008

We expect that Merck's HPV vaccine could be approved by 2006. It is likely that the vaccine would enter the market as a specialist pediatric vaccine, being recommended for all girls and boys aged five years. Like Prevnar, the ability to confer 100% protection could allow the product to be priced at a premium to other pediatric vaccines. We expect worldwide sales of \$100mn in 2006, \$450mn in 2007 and \$840mn in 2008. CSL, who developed the HPV vaccine technology, will be paid a royalty on sales. Aventis will have rights to market the Merck HPV vaccine through its Aventis Pasteur MSD joint venture company.

Great white hope yet to be realized

Therapeutic Vaccines

Therapeutic vaccines are designed to boost an individual's immune system to attack an existing illness, usually cancer. The idea is to generate a strong immune response against a cancer cell surface antigen. The notion of therapeutic vaccines holds great promise, but no one has been successful at putting this scientific concept into clinical practice.

Indeed, in 2H 2002, three different therapeutic cancer vaccine products failed in late stage phase III studies. Vical's Allovectin-7, Biomira's Theratope and Corixa's Melacine all produced disappointing results. The table below lists the therapeutic vaccines in phase III development. About 25 other companies are developing around 30 more therapeutic vaccines at earlier stages of clinical development.

We do not include therapeutic vaccines in our global vaccine market model, as we are still awaiting clinical proof of concept.

Table 14: Therapeutic Vaccines in Phase III Clinical Studies

Company	Drug	Indication	Comments
Antigenics	Oncophage	Metastatic melanoma (Stage IV)	Ph II - low response rate
Antigenics	Oncophage	Resected metastatic colorectal cancer	Ph II - good survival data
Aphton	Anti-G17 Immunogen	Metastatic stomach cancer	
Aphton	Anti-G17 Immunogen	Advanced pancreatic cancer	Ph II - good survival data
AVI BioPharma/SuperGen	Avicine (CTP-37)	Pancreatic cancer	
AVI BioPharma/SuperGen	Avicine (CTP-37)	Metastatic colorectal cancer	
Biomira	Theratope	Metastatic breast cancer	Ph III - interim review did not meet statistical significance for survival or time to progression
Biomira	Theratope	Metastatic colorectal cancer	
CancerVax	Canvaxin	Malignant melanoma	
CancerVax	Canvaxin	Refractory colorectal cancer	
Corixa	Melacine	Stage II melanoma	Ph III - no significant difference compared to control; survival increase in certain genotypes
Corixa	Melacine	Stage IV melanoma	Ph III - no survival difference compared to interferon alone
Dendreon	Provenge	Advanced prostate cancer	
Dendreon	Provenge	Prostate cancer	
Titan	CeaVac	Resected colorectal cancer	
Vical	Allovectin-7 (high dose, multi-injection)	Metastatic melanoma (Stage III and IV)	Ph II - low response rate
Vical	Allovectin-7 (low dose-10mg)	Melanoma	Ph III - missed primary endpoint of time to progression

Source: BioCentury Publications; Merrill Lynch

5. Initiation of Coverage: European Vaccine Companies

7 January 2003

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PowderJect Pharmaceuticals

Nothing to Sneeze At
BUY
Reason for Report: Initiation of Coverage

**Volatility Risk:
HIGH**

Price:	415p		
12-Month Price Objective:	514p		
Date Established:	03-Jan-2003		
Estimates (Mar)	2002A	2003E	2004E
Turnover	113.0	151.7	152.2
EBITDA	8.5	32.4	42.6
Pretax Profit (Loss)	1.2	21.6	31.2
Pre-g/w, except EPS	2.62	22.01	28.44
P/E	158.2	18.9	14.6
EPS Growth %	(109.6)	739.1	29.2
CFPS	10.0	32.5	41.0
Cash	7.2	14.3	32.8
Cash Burn	(4.9)	7.9	19.5
Free Cash Flow	5.0	21.6	27.3

Opinion & Financial Data

Investment Opinion – Local:	C-1-9
Mkt. Value (£ mn)/ Shares Outstanding (mn):	376 / 90.61
Book Value/Share (Mar-02):	131.328
Price/Book Ratio:	3.16
ROE 2003E Average:	14.6%
Net Debt/Net Equity:	21.9%
Est. 5 Year EPS Growth:	n/a
2003E P/E Rel. to Home Mkt:	164%

Stock Data

52-Week Range – Local:	603.50p-227.50p
Symbol / Exchange – Local:	PWJPF / London
Bloomberg / Reuters:	PJP LN / PJP.L
Exchange Rate:	GBP0.63/USD
Free Float:	75%

All figures are in Sterling except where otherwise noted.

Highlights:

- We initiate coverage of the UK vaccines company PowderJect with a Buy. An in-depth report is available.
- Our price objective is 514p, based on DCF analysis. This represents a potential upside of close to 25% to the current share price, and calendarised 03E and 04E PEs of 19x and 14x, respectively.
- PJP's key growth driver is Fluvirin flu vaccine, with 24% forecast compound sales growth (FY02A-FY06E).
- As PJP expands Fluvirin production capacity, we believe it will supply the gap in the US market left by Wyeth's recent withdrawal.
- Another growth driver is Dukoral, a travel vaccine set for European approval in mid-CY03.
- Combining top line growth with margin expansion, results in forecast EPS growth of 29% CAGR (FY03E-FY06E).
- Today we have also published an in-depth report on the Global Vaccines market.

Investors should assume that Merrill Lynch is seeking or will seek investment banking or other business relationships with the companies in this report.

Refer to important disclosures at the end of this report.

We initiate coverage of PowderJect with a Buy rating and a price objective of 514p.

Corporate Transformation

Over the past two years, PowderJect Pharmaceuticals has been transformed from a loss-making device company into a profitable vaccines business. In October 2000, PowderJect acquired the Medeva vaccines business from Celltech Pharmaceuticals, and in July 2001, it acquired SBL Vaccin of Sweden. We expect PJP to generate sales of £152mn and net profit of £19mn in FY03E.

■ M&A Activity

With the vaccines market dominated by larger pharmaceutical players, it is clear that stand-alone vaccine companies like PowderJect could prove to be attractive acquisition targets. This space has already observed the acquisition of Rhein Biotech by Berna Biotech of Switzerland. And more recently, PowderJect reported that a number of parties had made an unsolicited bid for its business. Although PJP and the potential acquirors did not enter into further discussions, it is likely in our view that both proposed and achieved M&A activity will continue to characterise the vaccines industry.

Influenza Vaccines – A Growth Market

We expect global sales of influenza vaccines to grow from an estimated \$966 mn in 2002E to over \$2 billion in 2007E, at a compound growth rate of 16% (see our in-depth report on Global Vaccines, published 7 Jan 03). Influenza vaccines is one of the more attractive vaccine markets, because individuals need to be vaccinated every year.

Over the next few years, there are three key factors that together will contribute to the rapid growth of the global flu vaccine market, in our view:

- Government policy recommendations that increase the target populations for flu vaccination.
- New delivery technology that will increase uptake and public awareness of the benefits of flu vaccination. In particular, we believe that the launch of Wyeth/MedImmune's nasally delivered FluMist will drive growth of the Flu vaccine market.
- We expect developing markets outside the US and Europe to expand as affluent middle classes choose to be vaccinated.

Fluvirin a Key Growth Driver

PowderJect's Fluvirin influenza vaccine is the company's most significant near term growth driver. We expect Fluvirin sales to grow from £66.7mn in FY02A to £157.2mn in FY06E, a four year CAGR of 24%.

With Wyeth's recent withdrawal from the US injectable flu vaccine market, PJP remains one of only two suppliers of injectable flu vaccine to the US market. Due to high barriers to entry, we expect that PJP and Aventis will remain the only two participants in the US injectable vaccine market until the 2005-06 flu season, at the earliest.

PJP plans to increase its flu vaccine production capacity from 27 mn doses in the current 2002-03 flu season, to over 35 mn doses in 2003-04 and over 40 mn doses in 2004-05. We believe that this increased capacity will flow directly to the bottom line, as PJP meets greater demand for flu vaccine in the US and other markets.

Travel Vaccines and Smallpox are Other Potential Upsides

■ Dukoral Runs Second to Fluvirin

After Fluvirin, PowderJect's traveller's diarrhoea vaccine Dukoral is the next key growth driver. Similar to flu vaccines, the Dukoral vaccine has a favourable sales profile because individuals need to be immunised for every journey. Unlike flu vaccines, however, this is not because the pathogen changes, but because immunity lasts for only 6-12 months. Therefore, manufacturing is much more straightforward, yielding attractive margins. We expect Dukoral to be approved in Europe in mid-CY03, and we believe that peak European sales of this drinkable vaccine could reach over £20mn by FY07E.

PowderJect sells Arilvax yellow fever vaccine in the UK, and is currently market leader with £3.8mn sales expected in FY03E. PJP plans to begin rolling out the launch of Arilvax throughout Europe starting in mid-2003, and we expect European sales of about £9mn by FY07E.

■ Biowarfare Premium

Following the terrorist events in the US in September 2001 and the anthrax scare in October 2001, there is heightened concern that terrorist organisations may use biological agents such as smallpox as weapons of bioterrorism. The US has led the efforts at establishing a smallpox vaccine stockpile, but most countries outside of the US do not currently possess smallpox vaccine sufficient to vaccinate every individual. We expect that other governments will use the same strategy as the US, i.e. (1) conduct pre-event vaccination of key "first response" health care workers and military personnel, and (2) build up a stockpile of enough doses to vaccinate every individual in the event that mass vaccination is ever required.

Most European nations previously used smallpox vaccines based on the Lister strain of vaccinia virus, so it is likely that only companies that can supply Lister-based vaccines will win new contracts, in our view. We believe that PJP will be one of only a few companies who will be able to supply the appropriate smallpox vaccine to European countries. PowderJect has rights from Bavarian Nordic to manufacture and supply its BN Lister vaccine to European countries. Acambis' smallpox vaccine is derived from the NYCBH strain, not the Lister strain favoured by Europe.

PJP is currently tendering for a new UK government contract to supply what we estimate to be 40 mn doses of smallpox vaccine, enough to create a stockpile to vaccinate every UK citizen. PJP won the first UK contract, and we believe it is well-positioned to win the next one. A new UK smallpox contract could be worth approximately £40 mn - £50 mn in potential revenues. We have not included these contract revenues in our forecasts, however.

Next Generation Vaccines

PowderJect has several vaccine development programs. The most advanced is a powder injection version of Fluvirin, which will enter phase II studies in 1H CY03. We expect 5 DNA vaccine programs to begin clinical studies in CY2003. The powder injection Fluvirin and the DNA vaccines will all be delivered using the patented PowderJect device

Financial Outlook

PowderJect achieved profitability in FY02, and we expect the company to remain profitable in the future.

Over the next 12-18 months, PJP has a number of opportunities to improve its operating margins. PJP inherited some rather unfavourable contracts with its purchase of Medeva Vaccines. A US Fluvirin distribution contract ends in March 2004, and the UK marketing contract with the Celltech sales force ends in September 2003. As a result, we expect operating margins to increase from 14% in FY03E to 25% in FY07E.

■ Three Year EPS Growth Forecast at 29%

Combining top line growth with forecast margin expansion, we expect EPS growth of 29% CAGR (FY03E-FY06E).

We Initiate Coverage with a Buy

Our price objective for PowderJect is 514p, based on DCF analysis, representing a potential upside of close to 25% to the current share price, and calendarised 03E and 04E PEs of 19x and 14x, respectively.

■ DCF Analysis Shows Significant Upside

Our discounted cash flow valuation is 514p per share. In our DCF model, we use a calculated WACC of 12.3%. Our discounted cash flow model includes forecasts from FY03 until FY08. We then fade free cash flow growth from 8% to 5% over 10 years and use a calculated exit EV/EBITDA multiple of 6.3x.

■ Risks to Price Objective

Risks to our price objective include the negative impact from the following potential events:

- If any of PJP's marketed vaccine products are recalled for quality control issues or safety concerns.
- If any of PJP's vaccine products in development are delayed or fail in clinical trials.
- Foreign exchange risk if the US Dollar weakens against GBP sterling – the majority of product sales are in the US (Fluvirin) and PJP's associated costs are in GBP.

Table 15: Vaccines Stock Universe

Company	Country	Symbol	Opinion	Local Price	Market Cap.		Earnings Per Share			P/E Ratio			5 Yr. EPS
					Local (bn)	US\$ (bn)	FY End	FY02 Est.	FY03 Est.	FY End	FY02 Est.	FY03 Est.	CAGR (E)
Aventis	France	AVENF	A-1-7	EUR53.6	42.45	37.238	2.07	2.64	3.24	25.89	20.3	16.54	23.7%
Baxter	USA	BAX	B-2-7	USD28.69	17.21	17.21	1.8	2.0	2.2	16.4	14.3	13.0	15.9%
GlaxoSmithKline	UK	GLAXF	B-1-7	1201p	70.5	100.6	72.41	78.19	83.22	16.59	15.36	14.43	14.1%
Merck	USA	MRK	A-2-7	USD58.25	131.99	131.99	3.14	3.14	3.42	18.55	18.55	17.03	3.0%
Wyeth	USA	WYE	B-2-7	USD38.79	51.63	51.63	2.18	2.23	2.45	17.79	17.39	15.83	10.0%
Acambis	UK	ACAMF	C-3-9	284p	0.28	0.45	(11.9)	2.9	29.3	n/a	97.3	9.7	n/a
Berna Biotech	Switzerland	BBITF	C-2-9	CHF12.40	0.38	0.27	2.4	0.1	0.0	5.2	106.0	338.3	(18.8%)
PowderJect	UK	PWJPF	C-1-9	403p	0.37	0.59	2.6	22.0	28.4	153.6	18.3	14.2	83.1%

Source: Merrill Lynch estimates

Table 16: PJP P&L Model

(£ millions except EPS)	FY03E							
	FY02A	1H03A	2H03E	FY03E	FY04E	FY05E	FY06E	FY07E
Turnover	113.0	88.0	63.7	151.7	152.2	184.5	199.6	209.0
Cost of Sales	(56.0)	(38.5)	(35.0)	(73.5)	(62.8)	(69.6)	(72.3)	(74.2)
Gross Profit	57.0	49.5	28.7	78.2	89.3	114.8	127.3	134.8
<i>Gross Margin %</i>	50%	56%	45%	52%	59%	62%	64%	64%
Total Operating Expenses	(56.5)	(26.5)	(30.0)	(56.5)	(59.3)	(73.8)	(78.6)	(81.3)
Selling and Distribution	(14.5)	(7.5)	(7.7)	(15.2)	(16.7)	(22.1)	(23.4)	(24.0)
<i>S&D as % sales</i>	13%	9%	12%	10%	11%	12%	12%	12%
Research and Development	(33.2)	(13.1)	(13.8)	(26.9)	(27.4)	(33.2)	(35.9)	(37.0)
<i>R&D as % sales</i>	29%	15%	22%	18%	18%	18%	18%	18%
General and Administrative	(8.8)	(5.9)	(8.5)	(14.4)	(15.2)	(18.4)	(19.4)	(20.3)
<i>G&A as % sales</i>	8%	7%	13%	10%	10%	10%	10%	10%
Goodwill Amortisation in G&A	(0.7)	(0.6)	(0.6)	(1.2)	(1.2)	(1.2)	(1.2)	(1.2)
<i>G&A ex-goodwill as % sales</i>	7%	6%	12%	9%	9%	9%	9%	9%
Other Operating Income/(Expense)	0.0	0.0	0.0	0.0	0.0	0.7	2.4	4.7
Arilvax Royalties from Acambis			0.0		0.0	0.7	2.4	4.7
Operating Profit	0.5	23.0	(1.3)	21.7	30.0	41.7	51.1	58.2
<i>Operating Margin %</i>	0%	26%	(2%)	14%	20%	23%	26%	28%
Pre-goodwill Operating Profit	1.2	23.6	(0.7)	22.9	31.2	42.9	52.3	59.4
Exceptionals	(0.5)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Profit (loss) on Disposals	(0.5)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Profit before interest & tax	(0.0)	23.0	(1.3)	21.7	30.0	41.7	51.1	58.2
<i>Pre-except PBIT</i>	0.5	23.0	(1.3)	21.7	30.0	41.7	51.1	58.2
<i>Pre-goodwill & Pre-exceptionals PBIT</i>	1.2	23.6	(0.7)	22.9	31.2	42.9	52.3	59.4
Net interest receivable	0.0	(0.4)	(0.9)	(1.3)	0.0	2.6	6.5	10.0
Pretax Profit	(0.0)	22.6	(2.2)	20.4	30.0	44.3	57.6	68.2
<i>Pre-except PTP</i>	0.5	22.6	(2.2)	20.4	30.0	44.3	57.6	68.2
<i>Pre-goodwill & Pre-exceptionals PTP</i>	1.2	23.2	(1.6)	21.6	31.2	45.5	58.8	69.4
Taxation	1.1	(1.5)	(0.1)	(1.6)	(5.4)	(10.2)	(17.3)	(20.5)
<i>Tax rate</i>	(223%)	7%	(6%)	8%	18%	23%	30%	30%
Net Profit	1.1	21.1	(2.3)	18.8	24.6	34.1	40.3	47.7
<i>Pre-except Net Profit</i>	1.6	21.1	(2.3)	18.8	24.6	34.1	40.3	47.7
<i>Pre-goodwill & Pre-exceptionals Net Profit</i>	2.3	21.7	(1.7)	19.9	25.8	35.3	41.5	48.9
Shares - basic (mn)	87.5	90.6	90.6	90.6	90.6	90.6	90.6	90.6
Shares - dil. (mn)	91.3	92.6	92.6	92.6	92.6	92.6	92.6	92.6
EPS (p)	1.3	23.3	(2.6)	20.7	27.1	37.7	44.5	52.7
<i>Pre-except EPS (p)</i>	1.8	23.3	(2.6)	20.7	27.1	37.7	44.5	52.7
<i>Pre-goodwill & Pre-exceptionals EPS (p)</i>	2.6	23.9	(1.9)	22.0	28.4	39.0	45.8	54.0
<i>Diluted EPS (p)</i>	1.2	22.8	(2.5)	20.2	26.5	36.8	43.5	51.5
<i>% Change Year over Year</i>								
Turnover	182.5%	70.2%	3.9%	34.2%	0.3%	21.2%	8.2%	4.7%
Cost of sales	139.5%	78.7%	1.5%	31.2%	(14.5%)	10.8%	3.8%	2.6%
Gross Profit	243.1%	64.1%	7.0%	37.2%	14.2%	28.6%	10.8%	5.9%
Total Operating Expenses	42.3%	1.1%	(1.0%)	0.0%	5.0%	24.3%	6.6%	3.4%
Selling and Distribution	271.8%	15.4%	(4.1%)	4.6%	10.3%	32.3%	5.5%	2.9%
Research and Development	7.4%	(20.6%)	(17.2%)	(18.9%)	1.7%	21.2%	8.2%	3.0%
General and Administrative	79.6%	84.4%	52.0%	63.8%	5.6%	21.2%	4.9%	4.7%
Operating Profit	(102.1%)	481.4%	(62.6%)	>1000%	38.3%	39.2%	22.4%	13.9%
Profit before interest & tax	(100.0%)	481.4%	(67.4%)	>1000%	38.3%	39.2%	22.4%	13.9%
Pre-except PBIT	(102.1%)	481.4%	(62.6%)	>1000%	38.3%	39.2%	22.4%	13.9%
Pretax Profit	(100.0%)	418.8%	(49.7%)	>1000%	47.1%	47.9%	29.9%	18.4%
Pre-except PTP	(102.4%)	418.8%	(43.2%)	>1000%	47.1%	47.9%	29.9%	18.4%
Net Profit	(105.8%)	363.1%	(32.9%)	>1000%	31.1%	38.8%	18.1%	18.4%
Pre-except Net Profit	(108.5%)	363.1%	(21.6%)	>1000%	31.1%	38.8%	18.1%	18.4%
EPS (p)	(105.2%)	326.5%	(36.7%)	>1000%	31.1%	38.8%	18.1%	18.4%
Pre-except EPS (p)	(107.5%)	326.5%	(26.0%)	>1000%	31.1%	38.8%	18.1%	18.4%

Source: Merrill Lynch estimates

7 January 2003

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Berna Biotech

A Jab in the Dark
NEUTRAL
Reason for Report: Initiation of Coverage

Volatility Risk:
HIGH

Price:	CHF12		
Estimates (Dec)	2001A	2002E	2003E
Net Sales (CHF mn)	292.5	184.1	198.7
EBITDA	75.8	10.1	20.1
Pretax Profit (Loss)	49.0	(7.3)	3.8
EPS	2.4	0.1	0.0
CFPS	5.5	(1.5)	0.5
Cash	262.8	74.9	75.0
Cash Burn	108.4	(186.6)	0.1
Free cash flow	123.0	(40.7)	16.0

Opinion & Financial Data

Investment Opinion – Local:	C-2-9
Mkt. Value (CHF mn)/ Shares Outstanding (mn):	364 / 30.36
Book Value/Share (Dec-01):	14.641
Price/Book Ratio:	0.82
ROE 2002E Average:	-3%
Net Debt/Net Equity:	-71.3%
Est. 5 Year EPS Growth:	-18.8%
2002E P/E Rel. to Home Mkt:	406%

Stock Data

52-Week Range – Local:	37.9-11.5
Symbol / Exchange – Local:	BBITF / Zurich
Bloomberg / Reuters:	BBIN SW / BBIZn.S
Exchange Rate:	CHF1.38/USD
Free Float:	96%

All figures are in Swiss franc except where otherwise noted.

Highlights:

- We initiate coverage on the Swiss vaccines company Berna Biotech with a Neutral recommendation. An in-depth report is available.
- Our DCF valuation indicates upside of about 15%, insufficient to justify a positive rating given the stock's high risk and near term uncertainties.
- Berna has been plagued by quality control issues with its travel vaccines Epaxal and Vivotif, and improving profitability depends on the success of their recent relaunches.
- Restructuring charges from the 2002 acquisition of Rhein Biotech will reduce 2002E reported net profit, and our forecast margin expansion relies on achievement of post-acquisition operating efficiencies.
- Berna's profitability is expected to be lower in 2002E than 2001, also due to one-off smallpox vaccine sales in 2001. After 2003E, however, we expect sustained net income growth of >20%.
- We may become more positive once there is evidence that the travel vaccines' franchise is back on track and Rhein successfully integrated.
- Berna reports under Swiss GAAP, which leads us to estimate certain undisclosed accounting items such as gross profit.
- Today we have also published an in-depth report on the Global Vaccines market.

Investors should assume that Merrill Lynch is seeking or will seek investment banking or other business relationships with the companies in this report.

Refer to important disclosures at the end of this report.

We initiate coverage of Berna Biotech with a Neutral recommendation. Our estimated DCF valuation indicates upside of about 15%, insufficient to justify a positive rating given the stock’s high risk and near term uncertainties. We would prefer to become more positive when there is evidence that the travel vaccines’ franchise is back on track and Rhein Biotech successfully integrated.

Focus on Vaccines

Berna Biotech began as the Swiss Serum and Vaccine Institute in 1898 but began restructuring in 1999 to focus on vaccines.

■ “Friendly Takeover” of Rhein

In July 2002, Berna acquired Rhein Biotech to form a combined company with a global reach. The majority of Rhein’s sales are to the public sector in developing countries, requiring a dedicated salesforce for supranational organisations. In contrast, Berna had focused primarily on the European market. In our view, Berna benefits from the merger largely due to the technology and infrastructure purchased. More importantly, Berna gains access to the rapidly growing vaccines market in the developing world. In the future, Berna may choose to manufacture vaccines for sale in Europe utilising Rhein’s low cost production facilities in Korea.

Travel, Flu and Hepatitis B

Following the acquisition, Berna markets five key vaccines as well as a portfolio of base vaccines. Vivotif, Orochol, Epaxal and Inflexal V are sold predominantly in the West whilst Hepavax-Gene is sold in over 60 developing countries and to supranational organisations. Hepavax was acquired with Rhein Biotech in July 2002 and now represents the company’s biggest selling single product. The recent alliance with Shire Pharmaceuticals enables Berna to market a sixth vaccine to developing countries, Fluviral for influenza, from 2003.

Table 17: Key Marketed Vaccines

Marketed Vaccines	Franchise and Disease	Sales in '06E
Vivotif	Travel – Typhoid fever	CHF17.5 mn
Orochol (Mutachol)	Travel – Cholera	CHF1.9 mn
Epaxal	Travel – Hepatitis A	CHF11.6 mn
Inflexal V	Influenza	CHF44.4 mn
Hepavax-Gene	Hepatitis B	CHF74.6 mn

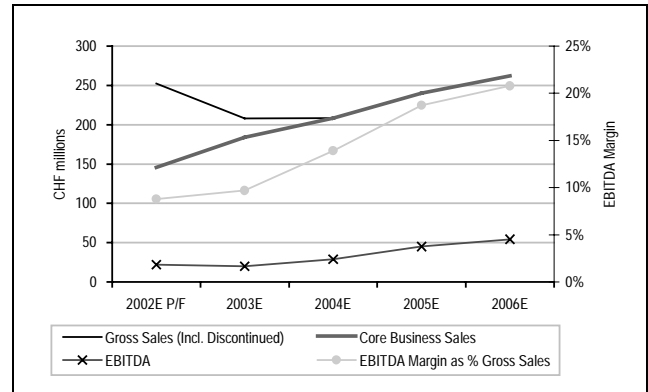
Source: Berna Biotech and Merrill Lynch estimates

Margin Expansion

We expect Berna to expand profit margins by rationalising its portfolio of vaccines and continuing to restructure its operations to focus on vaccines. The non-core businesses have lower gross margins and few operating synergies

with vaccines. We forecast EBITDA margins to improve as revenues from the core vaccines business grow. In particular, growing travel vaccine revenues improve gross margins as these products have relatively low costs of production and can be sold at comparatively high prices to travellers. In future years, we expect EBITDA margins to continue to expand as Berna launches new high margin vaccines, such as the specialist vaccine Aerugen in 2005/6. In addition, cost savings from the Rhein acquisition are anticipated to expand margins by 2005.

Chart 10: Expanding EBITDA Margins



Source: Merrill Lynch estimates

Growth Drivers

Revenues from the travel vaccines’ franchise drive growth in the near term. Epaxal was re-launched in 4Q02 following the recall by German authorities and Vivotif was re-released in October 2001 after US regulators banned the vaccine as it failed manufacturing quality control checks. According to our forecasts, these two vaccines represent over 85% of travel vaccine revenues. Hence, now that both are back on the market, we expect sales from this franchise to grow significantly from CHF14mn in 2002 to CHF32mn in 2006E.

We believe revenues from influenza vaccines will also drive near term growth. Virtually all influenza sales are currently due to Inflexal V, Berna’s virosomal flu vaccine. This product has improved immunogenicity compared to the conventional split and subunit influenza vaccines. We expect sales of influenza vaccines to grow at a five year compound annual growth rate of 23%, from an estimated CHF22mn in 2001 to CHF63mn in 2006.

Aerugen contributes to earnings in the longer term as it is expected to be highly profitable. It is a prophylactic vaccine for *Pseudomonas aeruginosa* infections in cystic fibrosis patients. We expect European approval in 2005 and US approval in 2006, and the vaccine is already sold on a named patient basis to European cystic fibrosis patients.

Rich Pipeline

Berna has a pipeline of around 20 vaccines, including five currently in Phase III trials and two in Phase II. This

portfolio should allow Berna to launch at least two new vaccines every year. The company has entered into a number of partnerships with some of its vaccines in development, including deals with Shire, Aventis and Chiron. Following the acquisition of Rhein Biotech, we believe Berna represents a more attractive partner due to its marketing infrastructure in Asia. This should enable Berna to demand a higher portion of the profits, whilst taking on a share of the marketing and product development costs.

We Initiate with a Neutral Rating

■ Profitability Declines in 2002E and 2003E

Profitability in 2002 and 2003 is expected to be lower than in 2001 due to one-off items and lower interest income on the smaller cash balance following the acquisition of Rhein. After 2003, we expect net income to report sustained growth of greater than 20%. We await evidence that the travel vaccines Epaxal and Vivotif are being successfully re-launched and confirmation that margin expansion can be achieved following the Rhein merger.

■ DCF Valuation Shows Modest Upside

Our estimated discounted cash flow valuation is nearly CHF14 per share using a WACC of 11.2% and exit EV/EBITDA multiple of 6.7x. This represents a 15% upside to the current share price.

Risks

In the near term we are concerned about profitability. The travel vaccines Epaxal and Vivotif must be successfully re-launched following the quality control issues in previous years. Improving profitability also depends on Berna successfully expanding margins following the Rhein merger. Additional risks are transparency issues, exposure to emerging markets and the need to find a US marketing partner for Aerugen.

Plenty of Potential

There are a number of potential upsides to current estimates and valuation. In the near term, Berna's remaining stockpile of smallpox doses could generate additional one-off revenues. On balance, we believe upside of at least CHF1.50 per share is reasonable assuming the stockpile is most likely to be sold in 2003(E) as there is currently significant pressure on governments to ensure they are prepared for the threat of bioterrorism. As the company reports financials, we should gain better visibility on the progressing margin expansion, which may allow us to increase our profitability estimates. Over the next few years, Epaxal may also surprise by gaining a greater than expected share of the European hepatitis A travellers' market.

Table 18: Vaccines Stock Universe

Company	Country	Symbol	Opinion	Local Price	Market Cap.		Earnings Per Share			P/E Ratio			5 Yr. EPS CAGR (E)
					Local (bn)	US\$ (bn)	FY End	FY02 Est.	FY03 Est.	FY End	FY02 Est.	FY03 Est.	
Aventis	France	AVENF	A-1-7	EUR53.6	42.45	37.238	2.07	2.64	3.24	25.89	20.3	16.54	23.7%
Baxter	USA	BAX	B-2-7	USD28.69	17.21	17.21	1.8	2.0	2.2	16.4	14.3	13.0	15.9%
GlaxoSmithKline	UK	GLAXF	B-1-7	1201p	70.5	100.6	72.41	78.19	83.22	16.59	15.36	14.43	14.1%
Merck	USA	MRK	A-2-7	USD58.25	131.99	131.99	3.14	3.14	3.42	18.55	18.55	17.03	3.0%
Wyeth	USA	WYE	B-2-7	USD38.79	51.63	51.63	2.18	2.23	2.45	17.79	17.39	15.83	10.0%
Acambis	UK	ACAMF	C-3-9	284p	0.28	0.45	(11.9)	2.9	29.3	n/a	97.3	9.7	n/a
Berna Biotech	Switzerland	BBITF	C-2-9	CHF12.40	0.38	0.27	2.4	0.1	0.0	5.2	106.0	338.3	(18.8%)
PowderJect	UK	PWJPF	C-1-9	403p	0.37	0.59	2.6	22.0	28.4	153.6	18.3	14.2	83.1%

Source: Merrill Lynch estimates

Activities

Berna Biotech recently acquired Rhein Biotech to form a vaccines company with operations in both Europe and Asia. Berna's key product franchises are in influenza, travel, and Hepatitis B vaccines. The company has undergone extensive restructuring to focus on vaccines in the future.

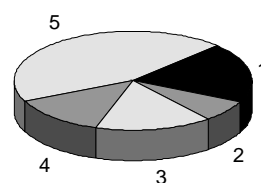
Profit & Loss

Y/E 31 Dec (CHF mn)	2001A	2002E	2003E
Gross Sales	303.8	192.8	208.1
Net Sales (CHF mn)	292.5	184.1	198.7
Total Operating Expenses	(206.0)	(170.5)	(171.7)
Operating Profit (Loss)	57.2	(4.9)	1.5
Net Interest	4.0	10.1	2.3
Extraordinaries	(12.1)	(12.5)	0.0
Pretax Profit (Loss)	49.0	(7.3)	3.8
Taxes	(7.6)	(1.1)	(0.8)
Net Income Before Extraord.	53.5	3.2	1.1
Net Income After Extraord.	41.4	(9.3)	1.1
EPS	2.4	0.1	0.0

Cash Flow

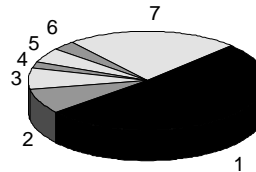
Y/E 31 Dec (CHF mn)	2001A	2002E	2003E
Operating Profit (Loss)	57.2	(4.9)	1.5
Depreciation & Amortisation	18.6	15.0	18.6
Change in Working Capital	52.2	(37.7)	8.3
Taxation	(7.6)	(1.1)	(0.8)
Operating Cash Flow	134.3	(32.0)	28.0
Cash Flow from Investments	(25.9)	(155.5)	(29.8)
Cash Flow from Financing	137.9	(0.4)	1.9
Increase in Cash	246.3	(187.9)	0.1
Cash Burn	108.4	(186.6)	0.1
Free cash flow	123.0	(40.7)	16.0

Sales by Franchise '02E



Franchise	%
1 Influenza	19.6
2 Travel	7.2
3 Hepatitis B	15.6
4 Other Vaccines	12.9
5 Discontinued Areas	44.6

Employees by Location '02E



Location	%
1 Switzerland	51.2
2 Spain	8.1
3 Italy	7.3
4 The Netherlands	2.5
5 Germany	5.4
6 Argentina	2.8
7 Korea	22.7

Balance Sheet

Y/E 31 Dec (CHF mn)	2001A	2002E	2003E
Net Intangible Assets	2.6	0.6	0.0
Net Tangible Fixed Assets	134.2	181.0	192.8
Investments	0.3	5.8	5.8
Other Current Assets	23.2	31.2	31.2
Cash	262.8	74.9	75.0
Total Assets	485.4	360.0	361.3
Shareholders Equity	366.6	242.3	243.4
Other L/T Liabs	0.0	0.0	0.0
Trade Creditors	24.1	19.1	19.6
Other Curr. Liabilities	69.8	27.1	24.9
Short Term Debt	1.3	0.0	0.0
Long Term Debt	0.0	24.7	24.7
Total Equity & Liabilities	485.4	360.0	361.3
Net Debt	(261.5)	(50.2)	(50.3)

7 January 2003

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Acambis

Plagued by Valuation
SELL
Reason for Report: Initiation of Coverage

**Volatility Risk:
HIGH**
Price - Local / ADR: 280.5p / \$44.99

Estimates (Dec)	2001A	2002E	2003E
Turnover	8.9	72.7	212.9
EBITDA	(10.3)	4.4	50.3
Pretax Profit (Loss)	(10.9)	2.8	49.0
Pre-g/w, except EPS	(11.86)	2.92	29.32
P/E	n/a	96.2	9.6
EPS Growth %	(3.9)	(124.6)	905.0
CFPS	(11.3)	4.2	30.7
Cash	22.2	19.8	101.3
Cash Burn	(15.9)	(9.5)	74.5
Free Cash Flow	(8.5)	1.9	77.3
ADR Pre-g/w, except EPS	\$-1.73	\$0.47	\$4.70
ADR CFPS	\$-1.64	\$0.68	\$4.93

Opinion & Financial Data

Investment Opinion – Local:	C-3-9
Investment Opinion – ADR:	C-3-9
Mkt. Value (£ mn)/ Shares Outstanding (mn):	275 / 98.05
Book Value/Share (Dec-01):	29.716
Price/Book Ratio:	9.44
ROE 2002E Average:	4.8%
Net Debt/Net Equity:	-11.2%
Est. 5 Year EPS Growth:	n/a
2002E P/E Rel. to Home Mkt:	757%

Stock Data

52-Week Range – Local:	379.00p-181.00p
52-Week Range – ADR:	\$55.3-\$28.4
Symbol / Exchange – Local:	ACAMF / London
Symbol / Exchange – ADR:	ACAM / New York
Bloomberg / Reuters:	ACMLN / ACM.L
Shares/ADR:	10.00
Exchange Rate:	GBP0.62/USD
Free Float:	83%

All figures are in Sterling except where otherwise noted.

Note: Due to currency factors, the investment opinion of the ADR may differ from the underlying share.

Highlights:

- We initiate coverage of vaccines company Acambis with a Sell rating. An in-depth report is available.
- Our risk-adjusted sum-of-the-parts analysis gives a valuation of 220p per share, or 20% below the current share price.
- Acambis is expected to be profitable from 2002E-2004E due to £330mn contracts to supply over 200mn doses of smallpox vaccine to the US.
- However, in 2005, we expect Acambis to revert to a loss-making company, due to a revenue gap prior to launch of any other significant vaccine products.
- Acambis may act as a proxy for bioterrorist risk, but we would be sellers into any potential price gains, because it is fundamentally overvalued.
- Even if the US government awards Acambis another 200 mn dose smallpox contract (which we believe is unlikely), this would represent an upside of 54p per share, which would bring Acambis' valuation in line with its current share price.
- Baxter owns 17% of Acambis and the two companies have a vaccine manufacturing alliance that could generate revenues for Acambis of \$200mn from 2004E – 2010E.
- Today we have also published an in-depth report on the Global Vaccines market.

Investors should assume that Merrill Lynch is seeking or will seek investment banking or other business relationships with the companies in this report.

Refer to important disclosures at the end of this report.

Executive Summary

We initiate coverage of Acambis with a Sell rating. Our sum-of-the-parts analysis indicates that Acambis is fundamentally overvalued.

Focus on Vaccines

Acambis was transformed into a dedicated vaccine company by its 1999 acquisition of the US company Oravax. Acambis develops novel vaccines against diseases that have no existing alternatives, and vaccines that offer significant benefits over the current protocol.

■ US Smallpox Contract Drives Profitability

In 2000 and 2001, Acambis won two major contracts with the US government to supply a total of over 200 million doses of smallpox vaccine. These contracts together are worth over \$500 mn in revenues, and have allowed Acambis to achieve near term profitability.

■ Travel Vaccines Suitable for Small Players

Acambis' particular focus is the travel vaccine market to immunise those visiting destinations where diseases are endemic. Large pharmaceutical companies dominate the biggest travel vaccine markets, such as hepatitis A and typhoid fever. In our view, the smaller travel vaccine markets, such as yellow fever and Japanese encephalitis, are available for exploitation by smaller companies. We suspect that these latter markets are too small for any big pharma competitors to actively defend their franchises from new entrants. In addition, successful marketing of travel vaccines often requires only a minimal sales force enabling companies such as Acambis to retain the full rights to the product, and the resulting profits, with minimal allocation of marketing resource.

■ A Baxter Vaccine Manufacturing Subsidiary?

In 2000, Acambis signed a strategic alliance with Baxter. Baxter agreed to purchase a total of \$40mn of Acambis shares, giving Baxter an eventual shareholding of around 20% (currently 17%). The alliance is a manufacturing agreement in which Acambis produces up to five anti-bacterial vaccines for Baxter, and receives royalties on sales. This agreement could generate revenues for Acambis of approximately \$200mn between 2004-2010E.

Smallpox Vaccines

Following the September 2001 terrorist events in the US and the anthrax scare in October 2001, there is a heightened concern about the threat of biological weapons. Particular focus has been given to smallpox, a deadly disease that can only be prevented by using a vaccine.

Acambis has won both of the US government contracts to supply over 200mn doses of smallpox vaccine. The company is developing two vaccines, ACAM1000 and ACAM2000 (in collaboration with Baxter), and we expect

these vaccines to receive regulatory approval in 2004. The Acambis smallpox vaccines are manufactured using modern cell culture technology, as opposed to existing stocks of smallpox vaccine produced decades ago by harvesting vaccinia virus from deliberately infected calves.

■ Financial Impact

The US government contracts push Acambis into profitability from 2002E to 2004E. They are expected to generate revenues for Acambis of nearly £330mn between 2002 and 2005, with over £200mn in 2003E alone. The contracts generate average gross margins of about 30%. In the long term, we expect smallpox stockpile maintenance revenues to be approximately £40mn annually.

■ More Major US Contracts Unlikely

While the US is waiting for delivery of the Acambis-Baxter vaccines, we believe there exist adequate supplies of older vaccines for limited vaccination or even mass vaccination in the event of a deliberate release of smallpox. The US still holds 15 mn doses of Dryvax, a calf-lymph vaccine made by Wyeth in the 1970's. In recent studies, Dryvax was shown to be potent at a 1/5 dilution, which means vaccine is available for vaccinating 75 mn people. The US also purchased from Aventis 85 mn doses of a similar calf-lymph vaccine manufactured in the 1950's, which in recent testing was shown to be fully potent, even at 1/5 or 1/10 dilutions. Therefore, the Aventis vaccine alone could be used to immunise over 400 mn people in a smallpox emergency.

Mass vaccination of the population prior to a smallpox outbreak is not favoured by the US government, due to safety concerns regarding side effects of the vaccine. We estimate that if all 280 mn Americans were vaccinated, 14,000 could be hospitalised, with over 400 deaths. New vaccines like the Acambis-Baxter ACAM2000 could only be shown to be safer than the older vaccines if trials were conducted in tens of thousands of volunteers. Therefore, we do not expect the newer vaccines to be used for pre-emptive mass vaccination, unless very large trials are conducted that show acceptable safety levels.

We do not believe that the US is likely to enter into another major smallpox vaccine supply agreement, as there are currently adequate smallpox vaccine supplies for mass vaccination in the event of an outbreak. Rather, we expect that the US government will purchase approximately 30 mn doses annually from Acambis under an existing maintenance contract, in order to maintain the stockpile and convert more doses from existing calf lymph vaccine to Acambis-Baxter's Vero-cell vaccine over time.

■ Acambis has the Wrong Strain for Europe

Most countries outside of the US do not currently possess smallpox vaccine stockpiles sufficient to vaccinate every individual. We expect that other governments will use the same strategy as the US, i.e. (1) conduct pre-event vaccination of key "first response" health care workers and

military personnel, and (2) build up a stockpile of enough doses to vaccinate every individual in the event that mass vaccination is ever required. In Europe, most nations previously used smallpox vaccines based on the Lister strain of vaccinia virus, so it is likely that only companies that can supply Lister-based vaccines will win major new contracts, in our view. The Acambis smallpox vaccine is based on the NYCBOH strain, so we believe Acambis will have a limited opportunity of supplying its smallpox vaccine to European nations.

Travel Vaccines

In addition to smallpox, Acambis has six other vaccines in clinical trials. Five of these are travel vaccines for yellow fever, Japanese encephalitis, typhoid fever, dengue and travellers' diarrhoea. Vaccines for yellow fever and JE are the most advanced.

■ Arilvax Approval Expected in 2004

We expect Arilvax yellow fever vaccine to be Acambis' first marketed travel vaccine, launched in mid-2004. Under the terms of a deal with PowderJect, Acambis funds the clinical studies required for US regulatory submission and has all US marketing rights for five years after launch.

When Arilvax is launched in the US, we expect it to take market share from Aventis' YF-VAX (current annual sales of approximately \$20mn), due to the longer shelf life and more convenient storage. Our peak sales forecast for Arilvax is \$21mn in 2009.

■ ChimeriVax-JE Approval Expected in 2007

ChimeriVax-JE is a single dose, live-attenuated vaccine against Japanese encephalitis. Acambis plans to begin a 5,000-patient Phase III trial in 2H03 following manufacturing scale-up activities. We expect Acambis to file ChimeriVax-JE for adult immunisation in late 2005, and the product could be launched in early 2007E.

We believe ChimeriVax-JE could achieve sales of \$80mn by 2010, due to its potentially better safety profile and longer immunity than existing marketed vaccines. Aventis markets the only approved JE vaccine JE-VAX in the US and Europe (current annual sales approximately \$100mn). JE-VAX immunity only lasts for about a year, and is derived from mouse brain (which can cause side effects).

We Initiate Coverage with a Sell

■ Overvalued According to Sum-of-the-Parts

Our risk-adjusted sum-of-the-parts analysis gives a valuation for Acambis of 220p per share, or 20% below the current share price (see Table 1).

We derived net present values of the cash flows for each of Acambis' major vaccine products: smallpox, Arilvax and ChimeriVax-JE. We also include the NPV of the royalty and manufacturing revenues anticipated from the Baxter contract. In our NPV models, we use a calculated WACC

for Acambis of 12.4%. We then adjusted the value of each product for the probability of reaching the market. We do not include NPV calculations for other products, as we believe these are too early stage to warrant inclusion. However, we have not included the significant negative NPV for Acambis' R&D expenditure of about £15-20 mn annually for early stage projects, which we believe would offset any positive NPV attributable to early stage products.

■ Losing Profitability

The US government smallpox vaccine contract revenues are expected to push Acambis into profitability between 2002 and 2004. However, in 2005 and beyond, revenues from maintaining the US smallpox stockpile are not sufficient for profitability to be sustained at our expected levels of operating expenditure. In our view, US Arilvax approval in mid-2004 will not generate sufficient top line growth to maintain profitability. We expect Acambis to be loss-making from 2005 until 2008, at which time Arilvax revenues revert to PowderJect, and ChimeriVax-JE sales drive the bottom line into the black again.

■ Cash Flow Deterioration

We expect Acambis to be significantly cash flow negative from now until 2008, apart from 2003. In this year, we expect the company to be cash flow positive as the majority of smallpox cash payments are received from the US government. As a consequence of expected future cash burn, we believe Acambis may have to seek short term funding facilities in 2007 of <£20mn.

■ Sell into Any Potential Biowarfare Gains

We acknowledge that Acambis is likely to act as a proxy for bioterrorist risk or events, but we would be sellers into any potential share price gains, because in our view the company is fundamentally overvalued. In addition, even though the smallpox contracts represent high revenue figures, the gross margin achieved is only 20%-40% (depending on the contract). We calculate that even if the US awards Acambis another 200 mn dose smallpox contract (which we believe is unlikely), this could represent an upside of 54p per share, which would bring Acambis' sum-of-the-parts valuation in line with its current share price.

Table 19: Acambis Sum-of-the-parts Analysis

Sum of the Parts	Value (£mn)	Probability	Adj. Value (£mn)	GBP per share
Arilvax NPV	12.6	0.8	10.1	10.2
Smallpox NPV	107.7	1.00	107.7	109.1
ChimeriVax-JE NPV	215.7	0.4	86.3	87.4
Baxter Contract Revenues	23.9	0.5	12.0	12.1
Net Debt	0.7	1.00	0.7	0.7
Valuation			216.9	219.6
Upside (Downside)				(20.7%)
Current Share Price (GBP)				277.0

Source: Merrill Lynch estimates

Table 20: Vaccines Stock Universe

Company	Country	Symbol	Opinion	Local Price	Market Cap.		Earnings Per Share			P/E Ratio			5 Yr. EPS
					Local (bn)	US\$ (bn)	FY End	FY02 Est.	FY03 Est.	FY End	FY02 Est.	FY03 Est.	CAGR (E)
Aventis	France	AVENF	A-1-7	EUR53.6	42.45	37.238	2.07	2.64	3.24	25.89	20.3	16.54	23.7%
Baxter	USA	BAX	B-2-7	USD28.69	17.21	17.21	1.8	2.0	2.2	16.4	14.3	13.0	15.9%
GlaxoSmithKline	UK	GLAXF	B-1-7	1201p	70.5	100.6	72.41	78.19	83.22	16.59	15.36	14.43	14.1%
Wyeth	USA	WYE	B-2-7	USD38.79	51.63	51.63	2.18	2.23	2.45	17.79	17.39	15.83	10.0%
Acambis	UK	ACAMF	C-3-9	284p	0.28	0.45	(11.9)	2.9	29.3	n/a	97.3	9.7	n/a
Berna Biotech	Switzerland	BBITF	C-2-9	CHF12.40	0.38	0.27	2.4	0.1	0.0	5.2	106.0	338.3	(18.8%)
PowderJect	UK	PWJPF	C-1-9	403p	0.37	0.59	2.6	22.0	28.4	153.6	18.3	14.2	83.1%

Source: Merrill Lynch Estimates

Activities

Acambis focuses on the development of vaccines. Following the events of September 2001, Acambis won both US government contracts for the supply of smallpox vaccine.

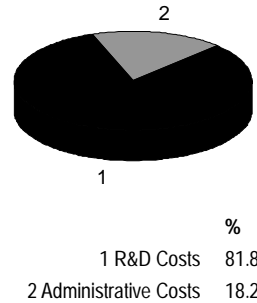
Profit & Loss

Y/E 31 Dec (£mn)	2001A	2002E	2003E
Turnover	8.9	72.7	212.9
Gross Profit	3.9	25.0	74.5
G&A Expenses	(3.5)	(4.2)	(4.5)
R&D Expenses	(12.6)	(18.9)	(23.0)
Total Operating Expenses	(16.1)	(23.1)	(27.5)
Group Operating Profit	(11.4)	2.8	47.5
Net Interest	0.6	(0.2)	1.5
Pretax Profit (Loss)	(10.9)	2.8	49.0
Taxes	0.1	0.0	(19.6)
Net Income Before Extraord.	(10.8)	2.8	29.4
Shares in Issue (end year) m	93.1	98.0	102.7
Pre-g/w, except EPS	(11.9)	2.9	29.3

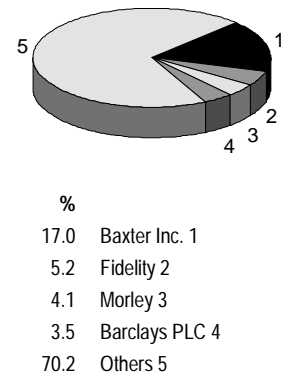
Cash Flow

Y/E 31 Dec (£mn)	2001A	2002E	2003E
EBITDA	(10.3)	4.4	50.3
Change in Working Capital	2.0	(3.2)	43.1
Operating Cash Flow	(8.0)	2.8	93.4
Maintenance Capex	(0.5)	(0.9)	(1.4)
Interest Recieved	1.0	0.0	1.5
Cash Flow from Investments	(8.9)	(12.3)	(5.6)
Cash Flow from Financing	17.0	7.0	7.0
Increase in YE Net Cash	20.9	(2.4)	81.5
Cash Burn	(15.9)	(9.5)	74.5
Free Cash Flow	(8.5)	1.9	77.3

Operating Expenses in 2002E



Major Shareholders



Balance Sheet

Y/E 31 Dec (£mn)	2001A	2002E	2003E
Net Goodwill	14.8	13.6	12.4
Net Tangible Fixed Assets	12.3	22.9	25.8
Investments	1.7	1.6	1.3
Inventories	0.0	37.8	5.7
Trade Debtors	5.9	36.9	0.1
Other Current Assets	7.9	7.9	7.9
Cash	22.2	19.8	101.3
Total Assets	64.8	140.5	154.5
Shareholders Equity	27.7	37.8	73.0
Minorities	n/a	n/a	n/a
Total Equity	27.7	37.8	73.0
Provisions	0.0	0.0	0.0
Other L/T Liabs	6.2	6.2	6.2
Trade Creditors	3.7	38.7	10.1
Other Curr. Liabilities	8.1	38.7	46.0
Short Term Debt	4.8	4.8	9.3
Long Term Debt	14.3	14.3	9.8
Total Equity & Liabilities	64.8	140.5	154.5
Net Debt	(3.1)	(0.7)	(82.2)

6. Vaccines Stock Universe

Table 21: Vaccines Stock Universe

Company	Country	Analyst	Symbol	Opinion	Local Price	Market Capitalization		Last FY End	Earnings Per Share			P/E Ratio			5 Yr. Est. EPS	
						Local (bn)	US\$ (bn)		FY End	FY02 Est.	FY03 Est.	FY End	FY02 Est.	FY03 Est.	Growth Rate	
Aventis	France	Culverwell	AVENF	A-1-7	EUR53.6	42.45	37.238	Dec 01	2.07	2.64	3.24	25.89	20.3	16.54	23.7%	
Baxter	USA	Lemaitre	BAX	B-2-7	USD28.69	17.21	17.21	Dec 01	1.8	2.0	2.2	16.4	14.3	13.0	15.9%	
GlaxoSmithKline	UK	Culverwell	GLAXF	B-1-7	1201p	70.5	100.6	Dec 01	72.41	78.19	83.22	16.59	15.36	14.43	14.1%	
Merck	USA	Risinger	MRK	A-2-7	USD58.25	131.99	131.99	Dec 01	3.14	3.14	3.42	18.55	18.55	17.03	3.0%	
Wyeth	USA	Risinger	WYE	B-2-7	USD38.79	51.63	51.63	Dec 01	2.18	2.23	2.45	17.79	17.39	15.83	10.0%	
Acambis	UK	Whittaker	ACAMF	C-3-9	284p	0.28	0.45	Dec 01	(11.9)	2.9	29.3	n/a	97.3	9.7	n/a	
Berna Biotech	Switzerland	Welford	BBITF	C-2-9	CHF12.40	0.38	0.27	Dec 01	2.4	0.1	0.0	5.2	106.0	338.3	(18.8%)	
PowderJect	UK	Whittaker	PWJPF	C-1-9	403p	0.37	0.59	Mar 02	2.6	22.0	28.4	153.6	18.3	14.2	83.1%	

Source: Merrill Lynch estimates

Appendix: Vaccines & Diseases

We have compiled a database of marketed vaccines and products in development to prevent over 25 contagious diseases. The information contained in this database is to the best of our knowledge, and is not an exhaustive list.

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Source: Merrill Lynch

Anthrax

■ Description

Zoonotic disease = disease of animals that can be transmitted to humans.

■ Cause

Gram-positive, spore forming bacterium *Bacillus anthracis*. Spores are markedly resistant to heat, cold, pH, desiccation, chemicals and irradiation.

Disease can also result from contact with animal products (hides, leather or hair).

■ Symptoms

Following germination at the infection site, the bacilli can also enter the blood and lead to septicemia.

3 forms depending upon the route of infection:

1. **Cutaneous anthrax:** Most common (>95% cases) arising when the bacterium enters a cut or abrasion on the skin. Itchy reddish-brown papule appears about 1-12 days after contact and soon develops a small vesicle.
Vesicle ruptures leaving a painless ulcer that typically develops a blackened eschar with surrounding swollen tissue. Systemic symptoms include swollen glands, fever, myalgia, malaise, vomiting and headache. Fatality rate ~20% without antibiotics.
2. **Gastrointestinal anthrax:** Begins 1-7 days after ingesting contaminated meat. Acute inflammation of intestinal tract with nausea, loss of appetite, vomiting and fever followed by abdominal pain, vomiting of blood and bloody diarrhoea.
May be involvement of the pharynx with sore throat, dysphagia, fever, lesions at the base of the tongue and regional lymphadenopathy. Fatality rate ~25%-60%.
3. **Inhalation anthrax:** Occurs 1-43 days after exposure to aerosolised spores. Non-specific initial symptoms include sore throat, mild fever, myalgia, coughing and chest discomfort lasting a few days.
Second stage develops abruptly with sudden onset of fever, acute respiratory distress with pulmonary edema and pleural effusion followed by cyanosis, shock and coma (meningitis also common). Fatality rate ~45%-90%.

■ Incidence

Occurs globally but most common in agricultural regions with inadequate control programs for anthrax in livestock (mostly wild and domestic animals, e.g. cattle, sheep, goats and other herbivores).

■ Treatment

Non-Vaccines

Antibiotics are effective against the germinated form but not the spore form of *Bacillus anthracis*.

Table 23: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
rPA102	Single component, recombinant <i>Bacillus anthracis</i> vaccine		VaxGen	Research	NIH development contract
BioThrax	Cell-free filtrates of avirulent <i>Bacillus anthracis</i> strain	Subcutaneous injection	Bioport Corp.	Approved	Requires 6 injections over 18 months

Source: Company Data

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Clostridium difficile (C. difficile)

■ Description

Ubiquitous in the environment, but can cause severe, and sometimes fatal, infections in “at risk” populations such as elderly inhabitants and hospital patients.

Gram-positive, spore-forming anaerobic bacterium responsible for 10%-25% of all cases of antibiotic-associated diarrhoea and almost all cases of pseudomembranous colitis (severe inflammation of large bowel).

Antibiotic-resistant bacterium.

■ Cause

Antibiotics may destroy normal bacteria in the gastro-intestinal tract allowing antibiotic-resistant C. difficile to establish itself in the colon where it can multiply rapidly without competing bacteria.

■ Symptoms

C. difficile produces toxins (A and B) that cause mucosal damage, inflammation and fluid secretion, resulting in diarrhoea and severe abdominal cramping.

■ Incidence

~3% healthy humans and 10%-20% hospital patients carry C. difficile.

~900,000 cases of C. difficile-associated diarrhoea ("CDAD") occur annually in the US and Europe (~300,000 in US). ~150,000 of these people relapse or do not respond to conventional treatment with antibiotics.

~60,000 patients suffer severe form of CDAD which can extend patient's hospital stay by ~21 days and increase treatment cost by ~\$10,000 on average.

■ Treatment

Non-Vaccines

Discontinuation of offending antibiotic and administration of alternative antibiotics, metronidazole or vancomycin.

Relapse from these treatments occurs in ~20% patients.

Vaccines

No vaccine is currently available.

Table 24: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
C. difficile vaccine	Active and passive vaccines		Acambis	Phase I	Target market is severe and moderate CDAD sufferers
Synsorb CD	Resin containing carbohydrates that bind to targeted toxins		Synsorb Inc	Phase III	

Source: Company Data

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Cholera

■ Description

Acute intestinal infection.

2 biotypes - Classical and El Tor strains.

■ Cause

Bacterium *Vibrio cholerae*, a toxin-producing pathogen.

Organism colonises the small intestine and excretes cholera toxin (CTX). These enterotoxins bind to intestinal cells and activate chloride channels resulting in fluid hypersecretion.

Transmitted by faecal-oral route by ingestion of contaminated food or water. Insects can physically carry bacteria between remote sites but humans are the only known host for cholera.

■ Symptoms

Watery diarrhoea - ranging from asymptomatic or very mild cases to very severe diarrhoea and other gastrointestinal symptoms.

Within hours of infection cholera can result in profound, rapidly progressing dehydration and eventual death if untreated.

Treated cholera has mortality rates ~1-5% whilst untreated cholera has ~50%-60% mortality rates.

■ Incidence

~3mn cases per year of which ~150,000 are fatal.

■ Treatment

Currently available injectable vaccines have not proved effective in preventing disease.

Non-Vaccines

Rehydration by replacing fluid and electrolytes.

Table 25: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
rPA102	Single component, recombinant <i>Bacillus anthracis</i> vaccine		VaxGen	Research	NIH development contract
BioThrax	Cell-free filtrates of avirulent <i>Bacillus anthracis</i> strain	Subcutaneous injection	Bioport Corp.	Approved	Requires 6 injections over 18 months
Dukoral	Cholera and ETEC vaccine	Oral	PowderJect	Approved in Nordic (EU/US Phase III)	2 doses (10 days and 1 day before travel). Annual renewal
Orochol	Single dose, live-alternated bacterial vaccine	Oral	Berna Biotech	Approved	

Source: Company Data

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Dengue Fever

■ Description

There are four immunologically related dengue virus serotypes (DEN 1, 2, 3 and 4) - an effective vaccine needs to represent all 4.

■ Cause

Mosquito borne viral infection. Infective mosquitoes are capable of transmitting the virus throughout their lives and females may transmit the virus to the next generation.

■ Symptoms

2 distinct clinical syndromes: 1. Dengue fever (debilitating acute disease characterised by fever, rash, headaches, muscle and joint pain) 2. Dengue haemorrhagic fever (characterised by prostration, bleeding and shock)

Without treatment DHF has fatality rates >20%.

■ Incidence

Endemic in more than 100 countries in Africa, the Americas, the eastern Mediterranean, south-east Asia and the western Pacific.

Continuing to spread, with an epidemic in Brazil that has affected more than 160,000 and resulted in more than 37 deaths since January 2001, and a current outbreak in Hawaii, the first in almost 50 years.

~2.5bn people are at risk and there are ~50mn cases of infection every year.

■ Treatment

No specific treatment currently available.

Vaccines

No vaccines available to prevent or treat dengue.

Table 26: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
ChimeriVax-Dengue	Single-dose, live attenuated tetravalent vaccine	Injectable	Acambis and Aventis Pasteur (hold WW rights)	Preclinical	Phase I proof-of-principle for 1 of 4 components. Target market is travellers, military and endemic populations
MVA-BN Dengue	MVA-BN vaccine to deliver multiple antigens from serotypes		Bavarian Nordic GlaxoSmithKline & Walter Reed Army Institute	Preclinical	
MAXY-1500	Tetravalent vaccine		Maxygen	Preclinical	Development was funded by US government
Dengue Vaccine	Recombinant sub-unit tetravalent vaccine		Hawaii Biotechnology Inc.	Preclinical	

Source: Company Data

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Diphtheria

■ Description

Contagious, airborne, toxin-producing infection caused by *C. diphtheriae*.

■ Cause

Diphtheria toxin secreted by *Corynebacterium diphtheriae*.

■ Symptoms

Formation of a grey resistant pseudomembrane in the lining of the mucous membrane of the upper respiratory tract and in the tonsils.

Some forms may be fatal (global mortality rate 5%-10%).

■ Incidence

Recent epidemics in industrialised countries have been due to poor coverage in adults (no boosters), population shifts and a lack of mass immunisation programs.

In 1998 WHO set the objective to reduce incidence in Europe to < 1 in 1,000,000.

Endemic particularly in Eastern Europe and Algeria.

■ Treatment

Vaccines

Mass immunisation has considerably reduced cases in the industrialised world - vaccine introduced in 1920s with widespread use in 1950s.

Vaccines obtained by detoxification of the toxoid with formalin.

Table 27: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Infanrix	Diphtheria, Tetanus and adsorbed acellular Pertussis vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
D.T. Vax	Adsorbed Diphtheria and Tetanus vaccine	i.m. injection	Aventis Pasteur	Approved	For children and newborns
Imovax d.T. adult	Adsorbed Diphtheria and Tetanus vaccine	i.m. injection	Aventis Pasteur	Approved	Booster that is administered every 10 years
D.T.COQ/D.T.P.	Adsorbed Diphtheria, Tetanus and Pertussis vaccine	i.m. injection	Aventis Pasteur	Approved	For children and infants
D.T.Polio	Diphtheria, Tetanus and Poliomyelitis vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRAct-HIB	Adsorbed Diphtheria, Tetanus, Pertussis and Hib vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRACOQ	Adsorbed Diphtheria, Tetanus, Pertussis and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	

Source: Company Data

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Helicobacter pylori (H. pylori)

■ Description

Probably the most common chronic infection of humans and the principal cause of peptic ulcers and chronic gastritis.
 Bacterium that lives on the stomach's lining or mucosal layer.

■ Cause

Transmission mechanism is not known.
 Mostly become infected in early childhood - average age lower in developing countries.

■ Symptoms

Most infected people do not have any symptoms and never develop illness.
 Causes ~90% duodenal ulcers and ~80% gastric ulcers.
 Long-term infection has been implicated as a cause of stomach cancer (2-6x more common in infected people).

■ Incidence

Affects ~50% world's population and ~66% >65 years old.
 10% Americans suffer from peptic ulcer disease during their lifetime (causes ~1mn hospitalisations and 6,500 deaths per year).

■ Treatment

No products prevent infection.

Non-Vaccines

Antibiotics eliminate H. pylori and acid-suppressing medications treat ulcers.

Vaccines

No vaccine currently available.

Table 28: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
H.pylori vaccine	Therapeutic and prophylactic vaccine		Acambis and Aventis Pasteur	Phase II	Target market is infected and at risk groups
HELIVAX	Therapeutic and prophylactic vaccine		Antex Biologics Inc	Phase II	

Source: Company Data

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Hepatitis A

■ Description

Hepatitis (inflammatory process in which the liver is the primary target) is caused by the viruses Hepatitis A, B, C, D, E and G.

Hepatitis A virus belongs to the picornavirus family. Only one serotype has been described.

■ Cause

Highly contagious disease with the predominant mode of transmission being person-to-person via the faecal-oral route.

■ Symptoms

Incubation period averages 28 days. Symptoms are mild and transient to severe and prolonged.

Preclinical period (10-50 days): asymptomatic, highest level of transmissibility.

Pre-icteric (prodromal) phase (3-9 days): loss of appetite, abdominal pain, nausea, vomiting, fever, diarrhoea, dark urine, pale stools, no jaundice.

Icteric phase (10 days of initial symptoms): jaundice in up to 88% of adults, as well as hepatomegaly and biochemical evidence of hepatocellular damage.

High mortality rate.

■ Incidence

Incidence of serious forms of Hep A is 0.5%.

Incidence is closely related to socioeconomic status. Endemic areas are Latin America, Asia and Eastern Europe.

Risk groups include travellers, medical personnel, populations in endemic regions, food handlers, active male homosexuals, intravenous drug users sharing needles and military personnel.

■ Treatment

Vaccines

Hep A immunisation is currently reserved for high-risk groups.

Whole virus vaccines inactivated with formalin or prepared with an adjuvant aluminium hydroxide.

For travellers, booster is taken after the trip to give three years immunity

Table 29: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Havrix	Inactivated whole virus vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	Aluminium hydroxide adjuvant and 2-phenoxyethanol preservative
Twinrix	Inactivated Hep A and recombinant Hep B vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	Aluminium adjuvant salts and 2-phenoxyethanol preservative
Avaxim	Inactivated vaccine	i.m. injection	Aventis Pasteur	Approved	Aluminium adjuvant
Vaqta	Inactivated whole virus vaccine	i.m. injection	Merck	Approved	Aluminium adjuvant
Epaxal	Virosomal vaccine	i.m. injection	Berna Biotech	Approved	

Source: Company Data

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Hepatitis B

■ Description

Hepatitis (inflammatory process in which the liver is the primary target) is caused by the viruses Hepatitis A, B, C, D, E and G.

■ Cause

Primary means of infection is sexual intercourse, intravenous drug use and blood transfusions with inadequately/not tested blood.

■ Symptoms

Incubation period 30-180 days.

Asymptomatic infection results in abnormal liver enzymes without jaundice (identified only by serological testing). ~25% adults with symptomatic disease has jaundice.

Serious consequences include acute massive hepatic necrosis, chronic active hepatitis and cirrhosis of the liver.

■ Incidence

~350mn chronic carriers of HBV worldwide. ~1mn deaths per year.

High endemicity in tropical Africa, southeast Asia and China.

2%-5% adult virus carriers develop chronic hepatitis. ~20% of these develop cirrhosis and possibly hepatocarcinoma.

90% newborns infected by their mothers become chronic carriers of the virus.

■ Treatment

Vaccines

First vaccines were prepared from plasma of infected subjects as the Hep B virus cannot be reliably produced in cell cultures.

New vaccines (first licensed in 1986) are based on recombinant proteins produced by introducing 1-3 genes of Hep B antigen into yeast/CHO cells.

Immunisation primarily recommended to high-risk groups (kidney insufficiency haemophiliacs, dialysis patients, organ transplant patients, infants born from carrier mothers, drug users, etc).

Vaccination prevents transmission from mother to baby, reduces HBV carrier rates and helps prevent liver cancer.

Table 30: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Engerix-B	Noninfectious recombinant DNA vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
Twinrix	Inactivated Hep A and recombinant Hep B vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
GenHevac B Pasteur	Inactivated suspension of HBs antigen vaccine	i.m. injection	Aventis Pasteur	Approved	
Recombivax HB	Recombinant vaccine	i.m. injection	Merck	Approved	
Comvax	Hib conjugate and Hep B recombinant vaccine	i.m. injection	Merck	Approved	
Bio-Hep-B	pre-S1, pre-S2 and S antigen Hep B vaccine	i.m. injection	Berna Biotech and Shire	Phase III in Europe	Developed by BTG and already marketed in Israel
Hepavax-Gene	Recombinant DNA Hep B vaccine	i.m. injection	Berna Biotech and Shire	Approved in Asia, South America, etc	Shire to register and sell in Europe

Source: Company Data

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Hepatitis C

■ Description

Major cause of acute hepatitis and chronic liver diseases.

A multivalent vaccine is required with simultaneous immunisation against several hepatitis C types.

■ Cause

Causes ~20% of all cases of viral hepatitis.

Spread by contact with the blood of an infected person.

■ Symptoms

Common symptoms include fatigue, jaundice, abdominal pain, appetite loss, intermittent nausea and vomiting.

60%-70% infections are asymptomatic.

Up to 80% progress to chronic infection of which 10%-20% develop liver cirrhosis and 1%-5% develop liver cancer.

■ Incidence

>170mn carriers of HCV worldwide mostly in Africa, south-east Asia and Latin America. ~12mn people in western countries are infected with the disease.

~3-4mn people are newly infected each year.

■ Treatment

Non-Vaccines

Anti-viral drugs - very expensive (several thousand dollars) so not used in many developing countries. Effective in 10%-50% people.

Vaccines

No vaccine is currently available.

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Influenza ("Flu")

■ Description

Acute respiratory tract infection. Family Orthomyxoviridae - two major types of influenza virus (A and B). The third type C is very rare.

Description: Type/Geographical origin/Strain number/Year of isolation (Subtypes H and N).

■ Cause

Easily spread via aerosols (coughing and sneezing), hand-to-hand contact and personal contact.

■ Symptoms

Fever, rhinitis, coughing, headaches and malaise. Incubation time ranges from 1-5 days (average of two days). Influenza virus renders subjects more vulnerable to other infections, including pneumococcus, staphylococcus or H. influenzae. Most common complication is pneumonia (mortality of influenza is often expressed as excess deaths due to pneumonia). Mortality rates in healthy >65 year olds are nine per 100,000.

■ Incidence

In temperate climates, influenza A epidemics occur almost every year during the winter vs. In tropical regions, disease may occur throughout the year often displaying a biannual pattern. Epidemics begin abruptly, peak over 2-3 weeks and last 2-3 months. During an epidemic the virus may infect 5%-20% of the entire population. Global epidemics/pandemics occur every 10-15 years due to major antigenic changes (antigenic shift) and are independent of season (most severe "Spanish flu" pandemic in 1918-1920 killed ~20mn people).

■ Treatment

Traditional definitive diagnosis using conventional lab tools (cultivation of virus) requires at least 3-4 days, but recent rapid viral or nucleic acid tests are becoming increasingly available.

Non-Vaccines

Antiviral drugs (e.g. M2 inhibitors against type A virus). (Neuraminidase inhibitors (act against both type A and type B viruses)).

Vaccines

Vaccines contain antigens from two A subtypes and one type B virus.

Table 31: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Fluarix	Split virion, inactivated influenza vaccine	i.m. injection	GlaxoSmithKline	Approved in UK	
Fluzone/Vaxigrip	Split virion, formaldehyde-inactivated influenza vaccine	i.m. injection	Aventis Pasteur	Approved	
FluINsure	Trivalent vaccine of purified protein conjugate	Intranasal	ID Biomedical	Phase II	
FluShield	Trivalent vaccine of types A and B (purified subvirion)	i.m. injection	Wyeth	Approved	Production stopped Nov '02
Influvac	Sub-unit inactivated influenza vaccine	i.m. injection	Solvay	Approved	
FluMist	Live-attenuated vaccine	Intranasal	MedImmune and Wyeth	Filed	
Inflexal V	Trivalent virosomal influenza vaccine	i.m. injection	Berna Biotech	Approved in Europe	
Influenza Vaccine	Trivalent virosomal influenza vaccine	i.m. injection	Solvay	Approved NL, Phase III	
Begrivac	Split virion, formaldehyde-inactivated influenza vaccine	i.m. injection	Chiron		Preservative-free
Fluad	Adjuvanted vaccine	i.m. injection	Chiron	Approved in 12 European countries	
Nasal flu	Trivalent virosomal influenza vaccine	Intranasal	Berna Biotech and Aventis	Phase I/II	
Fluvirin	Trivalent preservative-free vaccine	i.m. injection	PowderJect	Approved	
Influject	Vero cell (tissue culture) manufacture	i.m. injection	Baxter	Approved in NL, Phase III	
Fluviral	Split virion, inactivated influenza vaccine	i.m. injection	Shire Pharmaceuticals	Approved in Canada	Berna Biotech has international commercialisation rights

Source: Company Data

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Japanese Encephalitis (JE)

■ Description

Potentially fatal neurotropic viral infection.

Most important cause of viral encephalitis worldwide.

■ Cause

Mosquito-borne viral disease. Spread to humans by mosquitoes which transmit the virus from infected animals, notably pigs.

■ Symptoms

Usually starts as a flu-like illness with fever, chills, tiredness, headache, nausea and vomiting. Progresses to a serious infection of the brain.

~30% affected people die and many survivors have permanent neurological disabilities.

■ Incidence

Common in parts of Australia and Asia, including Japan, Korea, Taiwan, China, India and Thailand.

3bn people live in regions where JE is endemic (>70mn children are born in these regions each year) and ~14mn people from major developed countries travel to these regions every year.

~50,000 cases are diagnosed annually and ~10,000 die from the disease.

■ Treatment

No specific treatment.

Vaccines

Older vaccines prepared using mouse-brain tissue are used for universal immunisation of school-children in Japan, Korea and Taiwan, and for protection of travellers. These vaccines require multiple doses and frequent boosters.

World Health Organisation has identified the development of safer and less expensive vaccines against JE as a high priority.

Table 32: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
JE-VAX	Inactivated JE virus vaccine	Subcutaneous injection	Aventis Pasteur	Approved	Killed virus so low immune memory (~1 yr)
ChimeriVax-JE	Single dose, live-attenuated	Injectable	Acambis	Phase III	Target market is travellers, military and endemic populations (latter through partnerships)
			CJ Corporation (Korea)	Phase I	
			Rhein Biotech	Approved	Marketed to travellers in Europe

Source: Company Data

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Measles

■ Description

Contagious viral illness common in 3-10 year old children.

■ Cause

Morbillivirus (highly infectious member of the Paramyxoviridae family).

■ Symptoms

Seriousness is partly due to complications - respiratory (bronchitis, pneumonia) or neurological (convulsions, encephalitis).

■ Incidence

~50mn cases worldwide per year of which ~1.5mn are fatal.

One of the world's commonest infectious diseases that is still associated with a high mortality rate in many third-world countries.

WHO objective is to eradicate measles by 2007.

■ Treatment

Vaccines

Attenuated vaccines.

Licensed for use in the US in 1963.

In most industrialised countries, the triple MMR (measles, mumps, rubella) vaccine was introduced in Oct '98.

Table 33: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Priorix	Attenuated measles, mumps and rubella vaccine	Subcutaneous injection	GlaxoSmithKline	Approved in UK	
Rouvax	Attenuated measles vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
Rudi-Rouvax	Live attenuated measles and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
Trimovax Merieux	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
M-M-R II	Live measles, mumps and rubella vaccine	Subcutaneous injection	Merck	Approved	
2nd Gen MMR	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Berna Biotech	Phase III in Europe	

Source: Company Data

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Meningitis

■ Description

Meningococcal infections: more than 10 serogroups. The most common are A, B, C and Y; the more rare are X, Z and W 135.

Haemophilus influenzae: six distinct serotypes (a - f). b strain (Hib) found in large concentrations in cerebrospinal fluid and blood of afflicted young children.

■ Cause

Meningococcal infections or H. influenzae meningitis

■ Incidence

Meningococcal infections: Endemics characterised by sporadic cases are associated with groups B and C - found in countries with temperate climates in Europe and the US.

Widespread epidemics are most often associated with group A – found in tropical Africa. Most group A epidemics occur in the African meningitis belt (>15 countries).

Annual incidence is 0.6 per 100,000 in France but higher in Northern Europe, particularly Britain. Hib meningitis primarily affects children <5 years old.

Mortality rate ~10%. Mortality rate ~30%-40% in developing countries.

■ Treatment

Vaccines

Meningococcal infections: In Europe, bivalent vaccines combine purified and lyophilized capsular polysaccharides of meningococcus A and C. There are also vaccines for minority groups Y and W 135 but these aren't used in Europe.

Currently no vaccine for group B meningococcus.

Immunisation is necessary to prevent secondary meningococcal infection of individuals exposed to a primary case of infection. Induced immunity lasts at least three years.

Haemophilus influenzae: Incidence of Hib meningitis in Europe and the US considerably reduced after routine vaccination of children.

A number of Hib conjugate vaccines are used in >25 countries.

Table 34: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
ACWY Vax	Polysaccharide vaccine (groups A, C, W135 and Y)	Deep subcutaneous injection	GlaxoSmithKline	Approved in UK	
Hiberix	Hib polysaccharide vaccine	i.m. injection	GlaxoSmithKline	Approved in UK	
AC Vax	Polysaccharide vaccine (groups A and C)	Deep subcutaneous injection	GlaxoSmithKline	Approved in UK	
TETRAct-HIB	Adsorbed Diphtheria, Tetanus, Pertussis and Hib vaccine	i.m. injection	Aventis Pasteur	Approved	
Act-HIB	Hib polysaccharide vaccine	i.m. injection	Aventis Pasteur	Approved	
Meningococcal A+C	Polysaccharide vaccine (groups A and C)	Subcutaneous injection	Aventis Pasteur	Approved	
Menomune	Polysaccharide vaccine (groups A, C, W135 and Y)	Subcutaneous injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
Menactra	Polysaccharide vaccine (groups A, C, W135 and Y)		Aventis Pasteur	Phase III	2003 submission in US and Europe
HibTITER	Hib conjugate vaccine	i.m. injection	Wyeth	Approved	
Meningitec	Meningococcal meningitis vaccine	i.m. injection	Wyeth	Approved in Europe	
PedvaxHIB	Capsular polysaccharide vaccine	i.m. injection	Merck	Approved	
Comvax	Hib conjugate and Hep B recombinant vaccine	i.m. injection	Merck	Approved	
Menjugate	Conjugate vaccine (group C)		Chiron	Approved in Europe & Canada	

Source: Company Data

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Mumps

■ Description

Contagious viral infection.

■ Cause

Mumps virus belonging to the paramyxovirus family.

■ Symptoms

Most frequent is parotitis (inflammation of the parotid glands).

Most serious complications are neurological (temporary deafness, mumps meningoencephalitis) and glandular (orchitis, oophoritis, pancreatitis and mastitis).

■ Treatment

Vaccines

>10 vaccine strains have been used to prepare live attenuated vaccines.

Vaccine induces durable immunity and has considerably reduced the incidence.

In most industrialised countries, the triple MMR (measles, mumps, rubella) vaccine was introduced in Oct '98.

Table 35: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Priorix	Attenuated measles, mumps and rubella vaccine	Subcutaneous injection	GlaxoSmithKline	Approved in UK	
Trimovax Merieux	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
M-M-R II	Live measles, mumps and rubella vaccine	Subcutaneous injection	Merck	Approved	
2nd Gen MMR	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Berna Biotech	Phase III in Europe	

Source: Company Data

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Pertussis (Whooping cough)

■ Description

Highly contagious bacterial infection.

■ Cause

Infection by the bacteria *B. pertussis* or rarely *B. parapertussis*.

■ Symptoms

Persistent cough lasting >21 days characterised by long severe bouts of coughing.

Can be serious/fatal to infants <3 years old due to respiratory complications.

■ Incidence

~40mn cases worldwide per year of which ~36mn are in developing countries.

~62% cases in children <1 year old and 32% in infants <3 months old.

■ Treatment

Vaccines

2 types of vaccine:

1. "Whole-cell" vaccines composed of a mixture of bacterial suspensions inactivated by heat - used since 1950s and administered with diphtheria, tetanus and polio.
2. Acellular (subunit) vaccines containing one or more virulence antigens - used as a booster since 1990s but the initial infant immunisation must be with whole-cell vaccine.

Estimated worldwide coverage of the pertussis vaccine is 80%.

Immunisation has considerably reduced incidence.

Table 36: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Infanrix	Diphtheria, Tetanus and adsorbed acellular Pertussis vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
D.T.COQ/D.T.P.	Adsorbed Diphtheria, Tetanus and Pertussis vaccine	i.m. injection	Aventis Pasteur	Approved	For children and infants
TETRAAct-HIB	Adsorbed Diphtheria, Tetanus, Pertussis and Hib vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRACOO	Adsorbed Diphtheria, Tetanus, Pertussis and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	

Source: Company Data

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Pneumococcus

■ Description

Pneumococcal pathogen is responsible for pulmonary (pneumonia), ENT (particularly acute otitis media), neuromeningeal (meningitis) or systemic (bacteremia and septicemia) infections.

Growing resistance to antibiotics.

■ Symptoms

In young children, the primary risk is meningitis and to a lesser extent otitis. In the elderly, pneumonia is more common.

■ Incidence

WHO believe pneumococcal pneumonia accounts for 500,000-1.4mn deaths worldwide per year.

■ Treatment

Vaccines

Polysaccharide vaccine includes 23 different serotypes covering ~84% of all clinical infections.

Vaccine is recommended for at risk groups; patients with history of cardiac insufficiency or pulmonary infection, alcoholics with chronic liver problems, HIV and cancer patients, etc.

Table 37: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Pneumo 23	Polysaccharide vaccine	i.m. injection	Aventis Pasteur	Approved	
Prevnar	7-valent conjugate vaccine	i.m. injection	Wyeth	Approved	
Pnu-Imune 23	Polyvalent vaccine (23 most prevalent types)	i.m. injection	Wyeth	Approved	Production stopped Nov '02
Pneumovax 23	Polyvalent vaccine (23 most prevalent types)	i.m. injection	Merck	Approved	

Source: Company Data

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Poliomyelitis

■ Description

Acute viral infection.

■ Cause

Poliovirus – neuropathogenic virus transmitted orally.

■ Symptoms

Mild benign form (most frequent) manifested by feverish episode of diarrhoea followed by a clear liquid meningitis (non-paralytic poliomyelitis) or a flaccid paralysis of various muscular groups (paralytic poliomyelitis).

Acute flaccid paralyses are irreversible and are associated with muscular atrophy in the paralysed area. ~10% are fatal.

■ Incidence

Still exists in areas of Africa, southeast Asia, Indian subcontinent and Near East.

■ Treatment

Vaccines

Injectable vaccine composed of inactivated viruses (inactivated polio vaccine IPV) or oral polio vaccine composed of attenuated viral strains (OPV).

Oral vaccine is preferred (low cost) but this vaccine can lead to post-vaccinal paralysis due to a potential reversion of a vaccine strain to the wild virus.

Vaccines have considerably reduced incidence in industrialised countries.

Expected to be the second infection to be completely eradicated by immunisation.

Table 38: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Polio Sabin	Live oral vaccine	Oral drops	GlaxoSmithKline	Approved in UK	
D.T.Polio	Diphtheria, Tetanus and Poliomyelitis vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRACOQ	Adsorbed Diphtheria, Tetanus, Pertussis and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
Imovax Polio	Inactivated vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
Oral Polio Vaccine	Live oral trivalent vaccine	Oral drops	Aventis Pasteur	Approved	
T.Polio	Tetanus and Polio vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
Vaccin mot Polio	Polio vaccine	Subcutaneous injection	PowderJect	Approved in Sweden	

Source: Company Data

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Rabies

■ Description

Viral disease

■ Cause

Neurotropic virus often found in saliva of infected animals.

Bite wounds to the face, head, neck or hands must be taken seriously.

■ Symptoms

Irritation of the central nervous systems followed by paralysis and death.

Once the virus infects the brain the disease is always fatal.

■ Incidence

Greatest risk in Africa, Asia and Latin America from wild animals or more commonly stray dogs.

~40,000 deaths worldwide per annum (95% in Asia).

■ Treatment

Vaccines

Immunisation recommended to travellers if visiting a high-risk country, individuals with a professional risk, and people who have been in contact with an animal.

Prepared from cell cultures using various substrates - human diploid cell vaccine (HDCV), lineage of monkey kidney cells, chick embryo cells or fetus cells of the rhesus monkey.

Table 39: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Verorab	Purified inactivated vaccine	i.m. injection	Aventis Pasteur	Approved	For prevention in subjects with high risk
Favirab	Fragments of equine antirabies immune globulin vaccine	i.m. injection	Aventis Pasteur	Approved	Emergency immunisation after exposure
Imogam Rabies	Human rabies immunoglobulin vaccine	i.m. injection	Aventis Pasteur	Approved	Emergency immunisation after exposure

Source: Company Data

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Rubella (German measles)

■ Description

Contagious viral infection.

■ Cause

Rubella virus.

■ Symptoms

Harmless and mild in patients.

Potential danger is the risk of causing congenital defects during pregnancy.

■ Incidence

Inadequate vaccinal coverage has caused an epidemiological shift.

■ Treatment

Vaccines

Immunisation has considerably reduced incidence in industrialised countries.

Live attenuated vaccine prepared from cellular cultures usually administered as triple MMR (measles, mumps, rubella) vaccine.

Table 40: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Priorix	Attenuated measles, mumps and rubella vaccine	Subcutaneous injection	GlaxoSmithKline	Approved in UK	
Rudi-Rouvax	Live attenuated measles and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
Trimovax Merieux	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
Rudivax	Live attenuated vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
M-M-R II	Live measles, mumps and rubella vaccine	Subcutaneous injection	Merck	Approved	
2nd Gen MMR	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Berna Biotech	Phase III in Europe	

Source: Company Data

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Smallpox

■ Description

Smallpox has killed more people than any other infectious disease. It is a viral disease unique to humans. Officially only two remaining stocks of smallpox (US and Russia) but reports of illicit stocks from USSR's biological weapons programme during the Cold War.

■ Cause

Caused by Variola major virus. Only transmitted person to person, primarily by aerosolized saliva droplets expelled from an infected person. Contaminated clothing or bed linens also can spread the virus.

■ Symptoms

Symptoms appear approximately 12 days (range: 7 to 17 days) following exposure. Initially, high fever, fatigue, and head/back aches. A characteristic rash, most prominent on the face, arms, and legs, follows in 2-3 days - rash starts with flat red lesions ("maculopapular" rash). Lesions evolve at the same rate and become pus-filled, then begin to crust early in the second week. Scabs develop and then separate and fall off after about 3-4 weeks. Individuals are generally infectious to others from the time period immediately prior to the eruption of the maculopapular rash until the time of the shedding of scabs. ~30% mortality but patients who recover frequently have disfiguring scars. In 5%-10% patients, rapidly progressive malignant disease develops which is almost always fatal in 5-7 days.

■ Incidence

Last cases were reported in 1978.

■ Treatment

Immunity develops rapidly following inoculation with live viral vaccine. Generally protective even in people already exposed to smallpox and incubating the virus but not yet clinically ill, if given within three days after exposure. Successful immunisation results in the formation of a "pock" which heals to a small round scar. Vaccination not required in the US since 1972.

Non-Vaccines

No treatments available.

Table 41: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Dryvax			Wyeth		Production stopped in 1983
Elstree-BN			Bavarian Nordic		~\$48mn contracts in 2H02
ACAM1000	Live-viral vaccine	Injection with bifurcated needle	Acambis	Clinical and Production	1st USG contract 54mn doses produced by Acambis
ACAM2000	Live-viral vaccine	Injection with bifurcated needle	Acambis and Baxter (bulk manufacture)	Clinical and Production	2nd USG contract 155mn doses produced using serum-free cell culture
MVA-BN smallpox	Modified Virus Ankara vector vaccine		Bavarian Nordic	Phase I/II	

Source: Company Data

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Tetanus

■ Description

Severe toxin producing infection.

■ Cause

Anaerobic bacteria *Clostridium tetani* usually contracted following a benign injury or contaminated wounds.

Neonatal tetanus occurs when the umbilical cord is severed with an unsterilised instrument contaminated with tetani spores.

■ Symptoms

Severe muscular spasms and contractions.

Mortality rate is ~10%.

■ Incidence

In developing countries the incidence of neonatal tetanus is 0.5%-6.0% births.

Tetanus most commonly affects the over 50s.

■ Treatment

Vaccines

Immunisation has significantly reduced neonatal tetanus in many countries. Studies show 100% children born to mothers vaccinated during pregnancy possess protective antibodies.

All vaccines are based on simple or combined tetanus toxoids.

Many countries recommend vaccination soon after birth and boosters every 10 years.

Table 42: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Infanrix	Diphtheria, Tetanus and adsorbed acellular Pertussis vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
D.T. Vax	Adsorbed Diphtheria and Tetanus vaccine	i.m. injection	Aventis Pasteur	Approved	For children and newborns
Imovax d.T. adult	Adsorbed Diphtheria and Tetanus vaccine	i.m. injection	Aventis Pasteur	Approved	Booster that is administered every 10 years
D.T.COQ/D.T.P.	Adsorbed Diphtheria, Tetanus and Pertussis vaccine	i.m. injection	Aventis Pasteur	Approved	For children and infants
D.T.Polio	Diphtheria, Tetanus and Poliomyelitis vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRAct-HIB	Adsorbed Diphtheria, Tetanus, Pertussis and Hib vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRACOQ	Adsorbed Diphtheria, Tetanus, Pertussis and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
T.Polio	Tetanus and Polio vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
Tetavax	Adsorbed toxoid vaccine	i.m. injection	Aventis Pasteur	Approved	
Closet			PowderJect	Approved in UK	

Source: Company Data

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Travellers' Diarrhoea

■ Description

ETEC (enterotoxigenic E. coli) is estimated to be the most frequent cause of travellers' diarrhoea. Also caused by Campylobacter bacterium.

■ Cause

E. coli bacteria normally live in the intestine but the ETEC group produce toxins that stimulate the intestine's lining to secrete excess fluid. ETEC is transmitted via contaminated food or water.

■ Symptoms

Diarrhoea and abdominal cramping.
 Less common are fever, nausea, chills, loss of appetite, headache, muscle ache and bloating.
 Occasionally Campylobacter spreads to the bloodstream causing serious life-threatening infection.

■ Incidence

Endemic in 173 countries worldwide.
 ~75mn people annually travel to areas where contact with travellers' diarrhoea is likely. ~40% cases of travellers' diarrhoea are due to ETEC.
 ~30%-50% visitors to Latin America, Africa and Asia suffer from diarrhoea vs. ~10%-20% travellers to the Mediterranean, eastern Europe and Russia.
 In developed countries, Campylobacter infections have been increasing for several years (~2mn cases in the US every year).

■ Treatment

Non-Vaccines

Drinking water recommended and oral rehydration salts.
 Antibiotics can shorten illness duration but not generally recommended as ETEC is frequently resistant.

Vaccines

No vaccines currently available.

Table 43: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
HolaVax-ETEC	Live attenuated 5-strain vaccine	Oral	Acambis	Phase I	Target market is travellers, military and endemic populations (latter through partnerships)
Campylobacter vaccine	Live attenuated vaccine	Oral	Acambis	Pre-clinical	Expect clinical trials in '03. Target market is travellers, military and endemic populations (latter through partnerships)
Dukoral	Cholera and ETEC vaccine	Oral	PowderJect	Approved in Nordic (EU/US Phase III)	2 doses (10 days and 1 day before travel). Annual renewal
ACTIVAX	Multi-component vaccine for ETEC and Campylobacter Live attenuated vaccine		Antex Biologics Inc Avant Immunotherapeutics Inc	Phase I/II Research??	
ETEC vaccine		Oral	Microscience	Pre-clinical	

Source: Company Data

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Tuberculosis

■ Description

Mycobacteria infection.

Tuberculosis is responsible for more deaths than any other infectious disease (more than AIDS and malaria combined).

■ Cause

Most often Mycobacterium tuberculosis but rarely M. bovis or M. africanum.

Primarily a disease of the respiratory system and is spread by coughing/sneezing.

■ Symptoms

Patients may present without symptoms or in an extremely debilitated state.

Most TB patients have pulmonary disease. Extrapulmonary disease is usually seen in immunocompromised patients (e.g. HIV) and these patients have a higher risk for developing multidrug-resistant TB (MDR-TB) and miliary TB.

Cough that is worse in the morning (sometimes with hemoptysis), chest pain, breathlessness, night sweats, and signs of pneumonia. In advanced disease, there may be extreme weight loss.

■ Incidence

~1% population worldwide is infected every year (~3.8mn cases).

~2-3mn people are killed every year of which 100,000 are children.

An increased incidence in industrialised countries during the 1990s was attributed to the HIV epidemic, population migrations and poor living conditions of some segments of society.

■ Treatment

Diagnosis: Chest x-ray reveals cavitation, calcification (healed disease) and nodes in the upper lobes, but cannot confirm diagnosis.

Granulomas with caseation obtained in biopsy indicate the diagnosis. Sputum smears and cultures are useful in diagnosing pulmonary tuberculosis.

Non-Vaccines

Vaccines

BCG vaccine has nearly eradicated meningeal and miliary tuberculosis in countries with immunisation programs.

Table 44: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
BCG Vaccine	Seed derived from Strain 1077 vaccine	Intradermal	Aventis Pasteur	Approved	
BCG Vaccine		Intradermal	PowderJect	Approved in UK and Korea	

Source: Company Data

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Typhoid

■ Description

Typhoid fever remains life-threatening but can be treated.

Acute systemic infection.

■ Cause

Salmonella typhi bacteria principally transmitted by contaminated food and water. Usually spread by faecal-oral route.

Virulent strains pass through the stomach acid barrier, colonise the intestinal tract, penetrate the intestinal wall and then enter the lymphatic system and blood stream causing disease.

■ Symptoms

Sustained fever, severe headache, nausea, loss of appetite, constipation or diarrhoea.

Untreated the illness lasts for 3-4 weeks with 12%-30% fatality due to related complications.

■ Incidence

Endemic in 153 countries, mainly in south and east Asia, Africa and South America.

~16mn cases per year of which ~500,000 are fatal (almost entirely in the developing world).

Emerging disease as ~60x higher risk in HIV+ patients and the number of multi-drug resistant strains is increasing.

■ Treatment

Non-Vaccines

Treatment with antibiotics but ~25% cases are resistant to one or more antibiotic. Chloramphenicol is the gold standard but there are side effects.

Vaccines

Vaccines typically protect 50%-80% of recipients.

Berna's Vivotif (Ty21a) only current licenced oral typhoid vaccine in '99. Well tolerated (reported side effects include nausea, abdominal cramps and skin rash) but must be taken with a liquid <37C, every other day, on an empty stomach, 1 hour before a meal.

Table 45: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
HolaVax-Typhoid	Single-dose, live attenuated vaccine	Oral	Acambis (US and Can) and Berna	Phase II	
Vivotif	3 dose (4 dose in US) live attenuated Ty21a vaccine	Oral	Berna Biotech	Approved in NA, Africa, Asia and Europe	Recommended booster after 5 years. Age >6 years
Typhim Vi	Single-dose capsular polysaccharide vaccine	i.m. injection	Aventis Pasteur	Approved in US, Africa, Asia and Europe	Recommended booster after 2 years. Age >2 years
Typherix	Single-dose capsular polysaccharide vaccine	i.m. injection	GlaxoSmithKline	Approved in UK	Recommended booster after 3 years. Age >2 years
Typhoral L / Neotyf	Berna's Vivotif	Oral	Chiron	Marketed in Germany and Italy	
Ty800	Single-dose vaccine	Oral	Avant Immunotherapeutics Inc	Phase II	
Micro-Ty	Single-dose, live attenuated vaccine	Oral	Microscience	Phase I	

Source: Company Data

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Varicella (Chicken pox)

■ Description

Acute viral disease that is highly contagious.

■ Cause

Varicella-zoster virus (VZV).

■ Symptoms

Mild symptoms followed by an eruption appearing in crops and characterised by macules, papules, vesicles and crusting.

Symptoms are moderate when contracted by vaccinated individuals.

Dangerous to newborn infants, children with immune deficiencies and adults (mortality rate 25x higher than in children <13 years).

■ Incidence

Afflicts ~1% -4.5% vaccinated subjects every year vs. 85% of non-vaccinated children <10 years old.

~4mn cases in the US annually.

In tropical countries the highest incidence is observed in adolescents and young adults.

■ Treatment

Vaccines

Effective particularly in preventing a severe form of the disease in immunocompromised individuals.

Table 46: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Varilrix	Live attenuated varicella-zoster (Oka strain) vaccine	Subcutaneous injection	GlaxoSmithKline	Approved in UK	For healthy adults and adolescents not children
Varivax	Live attenuated varicella (Oka/Merck strain) vaccine	Subcutaneous injection	Merck	Approved	

Source: Company Data

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West Nile Virus (WNV)

■ Description

Virus grows in birds and is transmitted by mosquitoes from birds to humans and other mammals, e.g. horses and cows. May also now be transmitted by transplants and blood.

Virus can cause encephalitis or meningitis.

■ Cause

Mosquito borne viral infection.

■ Symptoms

Most infections are mild (fever, headache, body ache, rash and swollen lymph glands) but some severe (headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, weakness and paralysis).

Causes inflammation of the spinal cord and brain, can be fatal.

~7% people hospitalised with the infection die from it.

■ Incidence

First identified in the US in 1999 (62 cases of severe disease that year) but since carried by mosquitoes and migratory birds to a total of 41 (following 13 more in 2002) US states.

Commonly found in areas of Asia and Africa.

Segment of the population considered most at risk is aged 55+ (35mn people in the 28 states where West Nile has so far been identified).

■ Treatment

No vaccine, cure or specific therapy to prevent West Nile encephalitis exists but some symptoms can be treated.

US has sprayed pesticides to control mosquito populations.

Vaccines

No vaccines against West Nile virus.

Table 47: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
ChimeriVax-West Nile	Live attenuated vaccine	Injectable	Acambis	Preclinical	Target market is travellers and >55 years in US

Source: Company Data

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Yellow Fever

■ Description

Amaril virus transmitted by the Aedes mosquito.

■ Cause

Mosquito-borne virus of the family Flaviviridae.

■ Symptoms

2 phases: 1. Acute phase (fever, muscle pain, headache, shivers, loss of appetite, nausea and vomiting) 2. Toxic phase (jaundice, abdominal pain with vomiting, dysfunction of the liver/kidneys, bleeding and shock).

Most acute phase patients improve after 3-4 days but some enter toxic phase; half of these patients die within 10-14 days.

High fatality rate

■ Incidence

Endemic in tropical Africa and South America (48 countries now reporting cases). 33 countries are at risk in Africa (combined population ~468mn), nine South American countries and several Caribbean islands.

Incidence has increased significantly in recent years. ~200,000 cases of yellow fever a year with ~30,000 deaths.

Travellers to and inhabitants of endemic areas require vaccination.

■ Treatment

No specific treatment.

Non-Vaccines

Dehydration and fever can be corrected with oral rehydration salts and paracetamol.

Vaccines

Only YF vaccine currently approved for sale in the US is YF-VAX.

YF vaccines have been available for 60 years and are all live, attenuated vaccines derived from 17D strain. Immunity occurs within 1 week in 95% people and a single dose provides protection for 10 years to life.

Serious side effects extremely rare and generally only in children aged < 6 months so vaccine is not administered to this age group.

Table 48: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
YF-VAX/Stamaril	Single dose, live-attenuated 17D strain		Aventis Pasteur	US license in 1975	1yr shelf life and shipped on dry ice. Stamaril has longer shelf-life than US product
Arilvax	Single dose, live-attenuated 17D strain	Stabilised freeze-dried preparation	PowderJect and Acambis (US S&M only)	ACM Phase III in US. PJP markets in UK	2yr shelf life and only conventional refrigeration. Target market is travellers and military.
Yellow Fever vaccine	Single dose, live-attenuated 17D strain		Berna Biotech	Phase III	Europe only

Source: Company Data

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Pediatric Vaccines

Childhood immunisations are standard in Europe and North America.

Table 49: Vaccines

Name	Type	Formulation	Company	Development Stage	Comments
Pentacel	Diphtheria, tetanus, pertussis, polio and Hib vaccine	i.m. injection	Aventis Pasteur MSD (Joint Venture)	Phase III	US
Hexavac	Diphtheria, tetanus, pertussis, polio, Hib and Hep B vaccine	Fully liquid pediatric combination	Aventis Pasteur MSD (Joint Venture)	Approved in EU	
Priorix	Attenuated measles, mumps and rubella vaccine	Subcutaneous injection	GlaxoSmithKline	Approved in UK	
Trimovax Merieux	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Aventis Pasteur	Approved	
M-M-R II	Live measles, mumps and rubella vaccine	Subcutaneous injection	Merck	Approved	
Infanrix	Diphtheria, tetanus and adsorbed acellular Pertussis vaccine	i.m. injection	GlaxoSmithKline	Approved in US and UK	
Pediarix	Diphtheria, tetanus, pertussis, polio and Hep B vaccine	i.m. injection	GlaxoSmithKline	Approved in US	
D.T.COQ/D.T.P.	Adsorbed Diphtheria, Tetanus and Pertussis vaccine	i.m. injection	Aventis Pasteur	Approved	For children and infants
D.T.Polio	Diphtheria, Tetanus and Poliomyelitis vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRAct-HIB	Adsorbed Diphtheria, Tetanus, Pertussis and Hib vaccine	i.m. injection	Aventis Pasteur	Approved	
TETRACOO	Adsorbed Diphtheria, Tetanus, Pertussis and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
PENTAct-Hib	Adsorbed Diphtheria, Tetanus, Pertussis, Hib and Polio vaccine	i.m. injection	Aventis Pasteur	Approved	
2nd Gen MMR	Live attenuated measles, mumps and rubella vaccine	Subcutaneous injection	Berna Biotech	Phase III in Europe	

Source: Company Data

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Merrill Lynch is currently acting as financial advisor to King Pharmaceuticals Inc in connection with their purchase of three products from Aventis SA, which announced on December 31, 2002.

Investment Rating Distribution: Health Care Group (as of 31 December 2002)					
Coverage Universe	Count	Percent	Inv. Banking Relationships*	Count	Percent
Buy	97	54.80%	Buy	41	42.27%
Neutral	71	40.11%	Neutral	12	16.90%
Sell	9	5.08%	Sell	1	11.11%
Investment Rating Distribution: Global Group (as of 31 December 2002)					
Coverage Universe	Count	Percent	Inv. Banking Relationships*	Count	Percent
Buy	1110	43.46%	Buy	391	35.23%
Neutral	1236	48.39%	Neutral	319	25.81%
Sell	208	8.14%	Sell	43	20.67%

* Companies in respect of which MLPF&S or an affiliate has received compensation for investment banking services within the past 12 months.

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