Deutsche Bank
Markets Research

Industry
European Pharmaceuticals

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United Kingdom

Pharmaceuticals
Pharmaceuticals

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F.I.T.T. for investors

Tropical diseases; social responsibility, neglected market

Philanthropy today but an investment in over 40% of the world's population

One in three globally is at risk of malaria and the 17 'neglected tropical diseases', with dengue fever the fastest-growing threat. In this deep dive analysis, we highlight the resurgence of pharma industry engagement through WHO donations, flexible pricing and IP approaches, collaborative R&D, and investments in healthcare infrastructure and access. We see this as both 'doing the right thing' and a strategic investment in the customers of tomorrow, given that the tropics are home to over 40% of the world's population and include most of the least-developed countries. GSK, Novartis and Sanofi stand out in their efforts and long-term focus but Bayer and Roche also deserve praise.

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The massive scale of the problem

The WHO estimates that 1.2bn annually are at high risk of malaria (mainly in sub-Saharan Africa) while 1.4bn of the world's poorest are affected by 17 'neglected tropical diseases' (NTDs). The latter include dengue fever, which is fast becoming the most prevalent threat. 2014 has also seen a devastating and unprecedented outbreak of Ebola virus infection in Africa. The tragedy is that for many tropical diseases, effective treatment is available but inadequate healthcare access and poverty prevent the most vulnerable from benefiting.

Pharma industry engagement has grown dramatically

Intensified disease management goals from the WHO (including global targets for control/eradication of NTDs by 2020) have, together with the philanthropic efforts of organisations such as the Bill & Melinda Gates Foundation, led to a major uplift in the funding, treatment of, and research into, tropical diseases. The pharma industry has embraced this, stepping up efforts to donate product, collaborate in R&D, improve access and strengthen infrastructure in affected countries. The London Declaration on NTDs in 2012 was a galvanizing event.

GSK, Sanofi and Novartis have major efforts underway to combat tropical disease

In our large-cap coverage, we highlight GSK, Sanofi and Novartis (in that order) as showing outstanding commitment to tropical diseases. GSK and Sanofi have highly pro-active, industry-leading approaches as well as a broad range of relevant drugs and vaccines (they jointly lead in the supply of vaccines for the developing world). Each has dedicated market access units for the poorest nations and multiple support programs to improve health education, training and capacity. Their dedicated R&D spend ($100m+ each) substantially exceeds that of peers. Novartis meanwhile deserves particular credit for its central role in the supply of anti-malarial drugs in Africa and its 'Novartis Malaria Initiative' access program. Bayer and Roche have lower levels of investment but play key roles respectively in the provision of drugs for sleeping sickness and HIV/AIDS.

Vaccines for malaria (GSK) and dengue (Sanofi) set to advance the fight

Vaccines constitute a highly cost-effective form of healthcare and late-stage candidates for malaria and dengue could each be launched from late-2015. GSK's potential malaria vaccine has sub-optimal efficacy (c.30%) in infants but will be priced on a not-for-profit basis and could be a key weapon in the fight against a disease that kills 1,300 children a day. Meanwhile success in two large-scale pivotal trials of Sanofi's dengue vaccine (showing c.60% efficacy and major public health benefits) suggests that, based on projected demand, this could become the top-selling vaccine in the developing world (c.€1bn pa).

Companies Featured

GlaxoSmithKline (GSK.L),GBP1,432.50			Hold
	2013A	2014E	2015E
DB EPS (GBP)	106.46	93.90	97.30
P/E (x)	15.0	15.3	14.7
EV/EBITA (x)	15.7	17.0	16.4

Bayer AG (BAYGn.DE),EUR105.60			Buy
	2013A	2014E	2015E
DB EPS (EUR)	5.61	6.00	7.01
P/E (x)	14.9	17.6	15.1
EV/EBITA (x)	13.8	17.0	15.5

Novartis (NOVN.VX),CHF87.05			Hold
	2013A	2014E	2015E
DB EPS (USD)	5.01	5.26	5.85
P/E (x)	14.6	17.8	16.0
EV/EBITA (x)	16.1	18.0	20.0

Roche (ROG.VX),CHF270.90			Buy
	2013A	2014E	2015E
DB EPS (CHF)	14.27	14.31	14.62
P/E (x)	16.2	18.9	18.5
EV/EBITA (x)	12.5	15.1	13.8

Sanofi (SASY.PA),EUR85.77			Buy
	2013A	2014E	2015E
DB EPS (EUR)	5.05	5.23	5.80
P/E (x)	15.2	16.4	14.8
EV/EBITA (x)	20.1	19.2	15.0

Source: Deutsche Bank

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Executive summary

Socially responsible, long-term business sense

The massive scale of the problem

Aggressive and far-reaching disease management goals from the World Health Organization (WHO) have, together with the philanthropic efforts of organisations such as the Bill & Melinda Gates Foundation, resulted over the past decade in an intensification of the funding and supply of medicines for - and research and development into - tropical diseases. These include the more common diseases (malaria, TB) as well as 17 designated 'neglected tropical diseases' (NTDs; dengue, sleeping sickness etc; Figure 1) for which the WHO has set out individual global targets to control or eradicate by 2020.

The scale of the challenge is enormous: some 1.2bn annually are at high risk of malaria (mainly in sub-Saharan Africa) while roughly one in three of the world's population is at risk of NTDs and 1.4bn of the world's poorest are affected by these. 2014 has also seen an unprecedented outbreak of Ebola virus infection in Africa. The tragedy is that for many tropical diseases (unfortunately not Ebola or dengue), effective treatment is available but inadequate healthcare access, poverty and conflict prevent the most vulnerable from benefiting. For example, despite a huge uplift in the supply of effective combination anti-malarial drugs, up to half of malaria patients in Africa do not have adequate access to public health services and <20% of children with malaria and fever receive treatment. Investment in education, sanitation and healthcare access is as crucial as the supply of drugs and vaccines in seeking to meet WHO goals.

Figure 1: Neglected Tropical Diseases (classified by infectious organism sub-type)

Virus
Dengue
Rabies

Protozoa (single-celled organisms)
Chagas disease
Human African trypanosomiasis *(sleeping sickness)*
Leishmaniasis

Bacteria
Buruli ulcer
Leprosy
Trachoma
Yaws

Helminth (worms and flukes)
Cysticercosis/Taeniasis *(tapeworms)*
Dracunculiasis *(Guinea worm disease)*
Echinococcosis
Schistosomiasis *(bilharzia)*
Lymphatic filariasis *(elephantiasis)*
Onchocerciasis *(river blindness)*
Soil-transmitted helminthiases *(intestinal worms)*
Food-borne trematodiases

Source: 'Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation' (WHO, 2012), Deutsche Bank

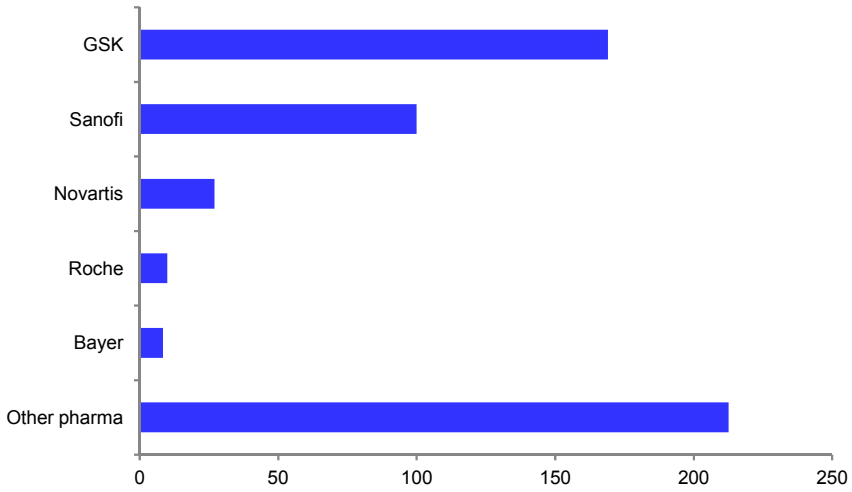
Pharma industry engagement has grown dramatically

The pharmaceutical industry has embraced this renewed focus on diseases of the developing world, stepping up efforts to donate product, improve access to its medicines/vaccines (through tiered/affordable pricing and, in situations of critical need, waiving patent rights and/or engaging in voluntary licensing), collaborating in R&D and investing in the health infrastructure of affected countries. The London Declaration on NTDs in 2012, which accompanied publication of the WHO's 2020 roadmap, was a galvanizing event, bringing together stakeholders from the pharmaceutical/medical industry (including Bayer, GSK, Novartis and Sanofi, among the European large-cap pharma companies), governmental and philanthropic organisations. This resulted in increased donations, funding and a reversal of a declining trend in R&D spend.

Today the pharma industry's activities in this area can be described as philanthropic in nature as the associated revenues are minimal (<1% of group) and the costs of donations, access programs and R&D typically far outweigh these. GSK, for example, donated drugs last year with a wholesale value of over £500m and spent in the region of £100m on dedicated R&D, we estimate. There is an argument that even more could be done (in particular, pharma R&D spend on tropical diseases of just over $500m pa remains a minor component of total industry spend of >$130bn pa). However, we see the industry's efforts – especially in regard to strengthening local healthcare capacity - as a clear case of 'doing the right thing' while making a strategic long-term investment in the customers of tomorrow. The tropics are home to over 40% (and rising) of the world's population and include 43 of the 48 least-developed countries (LDCs). Although tricky issues surrounding patent recognition will clearly need to be negotiated, economic growth in the decades ahead will inevitably see many of these nations becoming increasingly important commercially to the pharma industry. A 2013 study by PwC ("*World in 2050*"), for example, projected that Indonesia, Nigeria and Vietnam will have a combined GDP of c.$13tr by 2050, an eight-fold increase over the official figures for 2013, with the latter two countries joining Indonesia in the world's top 20 economies.

In differentiating between the efforts of pharma industry players in the developing world (and specifically tropical diseases), we believe the European large-cap companies tend to have a greater focus on investing in local healthcare capacity and building sustainable businesses in the affected regions whereas their US peers tend to focus more on the purely philanthropic aspects (bulk WHO donations etc), although there are exceptions to this (notably Johnson & Johnson). We think this longer term strategic approach is key to any SRI appraisal of the industry and of the individual pharma companies.

Figure 2: Estimated tropical disease R&D spend (2013)



Note: GSK based off average spend 2010-2011, Novartis and Bayer actual figure, Sanofi , Roche and pharma overall are estimates by DB
Source: Company data, G-FINDER, Deutsche Bank

Ranking the companies: GSK, Sanofi and Novartis stand out

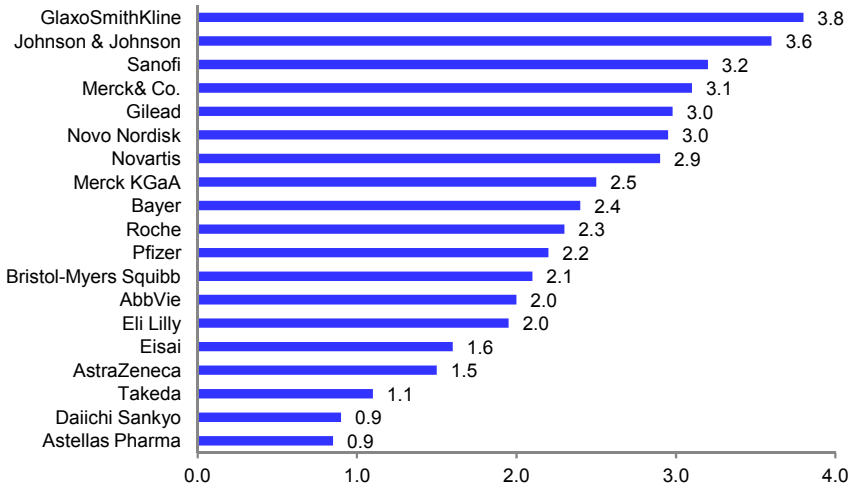
Within our large-cap coverage, we believe GSK, Sanofi and Novartis (in that order) stand out in their efforts to combat tropical diseases and long-term focus but Bayer and Roche also deserve praise (AstraZeneca and Novo Nordisk have minimal exposure and so are not discussed in detail in this report):

- **GSK** (rated Hold) has demonstrated the highest commitment to tropical diseases, in our view. It supplies a broad range of drugs and vaccines relevant to the developing world (including for tropical diseases), both via bulk donation to the WHO (for lymphatic filariasis) and at tiered prices to public and private markets, and is consistently in the vanguard of industry initiatives. For example, it was a signatory to the London Declaration on NTDs, a founder of the WIPO Re:Search open-access database for neglected disease R&D, and has shown a highly flexible approach towards IP (it does not enforce patents in developing countries). In particular, we highlight its novel Developing Countries and Market Access (DCMA) unit which caps its drug prices for LDCs at 25% of those charged in developed countries and reinvests 20% of profits into local healthcare projects. Its innovative approach is also evident in its R&D activities, with a dedicated DDW (diseases of the developing world) Open Lab in Spain and a second Open Lab planned as part of a strategic investment program in Africa. Its key pipeline project is the first malaria vaccine (discussed below) and it recently started volunteer studies on a candidate Ebola vaccine. We note that GSK's spend on R&D into NTDs has in recent years accounted for around a third of entire industry spend (Figure 2).
- **Sanofi** (rated Buy) comes a close second to GSK in its commitment to tropical diseases, in our view. As the overall industry leader in EMs, the company similarly supplies a broad range of drugs and vaccines for the developing world and has taken a lead role in key initiatives (London Declaration, WIPO Re:Search, Medicines for Malaria Venture etc). It is a key donor of drugs for Human African Trypanosomiasis (sleeping sickness) and operates an innovative Access to Medicines department as well as the Sanofi Espoir Foundation (an award-winning organisation which aims to reduce health inequalities via development aid projects and responses to humanitarian emergencies). In total, Sanofi operates 260 access to healthcare programs, benefiting 177m people globally. In terms of patents, Sanofi's policies are similar to the best practice of peers such as GSK (eg, it does not file/enforce patents in LDCs). The company maintains an active involvement in R&D for tropical diseases, its highest profile product being a potentially groundbreaking dengue vaccine, which could well become the top-selling vaccine in the developing world (with peak sales of €1bn plausible) given the successful outcome of two recently-reported, pivotal Phase III trials. We estimate Sanofi spent approximately $100m on tropical disease R&D in 2013, putting it second only to GSK.
- **Novartis** (rated Hold) deserves significant credit for its central role in the supply of combination anti-malarial drugs (ACTs) in Africa (it has been the main donor to the WHO since 2001) and its extensive 'Novartis Malaria Initiative' program (one of the largest access-to-medicine programs). It also supplies a range of other relevant products including vaccines for rabies and drugs for TB and is the key donor of multi-drug therapy for leprosy and the anti-fluke drug triclabendazole. Novartis was a signatory of the London Declaration and a founder member of WIPO Re:Search and it does not file or maintain patents in LDCs. It operates two dedicated R&D units, the Novartis Institute for Tropical Diseases (NITD) and the Novartis Vaccines Institute for Global Health (NVGH), although the latter will transfer to GSK following its planned acquisition of Novartis' vaccines business (expected in 1H15). In line with Novartis' key role in the provision of malaria treatment, the NITD's main projects are two novel anti-malarial drugs in Phase II.

- **Bayer** (rated Buy) has a longstanding involvement in tropical diseases and was a signatory to the London Declaration on NTDs. It is a key supplier to the WHO of bulk donated medicines to treat Human African Trypanosomiasis (sleeping sickness) and Chagas disease and has developed specialised access programs for each, while its CropScience arm supplies vital insecticides for vector (mainly mosquito) control. While these efforts are laudable, we rank it below the foregoing companies as it has a lesser financial commitment, notably in terms of its modest R&D spend in the field (<$10m).
- **Roche** (rated Buy) supplies over 20 off-patent anti-infective drugs for tropical diseases (for Chagas, malaria, TB etc) at very low prices and has gained acclaim for a unique technology transfer initiative in HIV (whereby it advised and trained 13 companies, mostly in Africa, on how to manufacture its HIV drug saquinavir to GMP standards). We deem its overall commitment to tropical diseases as significantly lower than that of GSK, Sanofi and Novartis as it is not involved in donation programs and did not participate in the London Declaration. Furthermore it does not have any specific R&D activities in this area.

In support of our conclusions we would highlight the findings of the Access to Medicine Foundation (a not-for-profit organization which is part-funded by the Bill & Melinda Gates Foundation). This publishes a biennial Index which ranks the 20 largest pharma companies on their access to medicines policies and practices in low- and middle-income countries (note: this is not specific to tropical diseases). An update is due in November but in its 2012 report the European large-cap companies were well represented with GSK and Sanofi ranked first and third respectively (Figure 3), with Novo Nordisk (#6), Novartis (#7), Bayer (#9) and Roche (#10) also in the top ten. GSK and Sanofi were the most highly ranked in terms of philanthropic activities and dedicated R&D. Full details are available on the www.accesstomedicineindex.org website.

Figure 3: Rankings in the Access to Medicine Index



Source: Access to Medicine Index, 2012

Two products to watch: vaccines for malaria (GSK) and dengue (Sanofi)

Vaccination is often the most cost-effective form of healthcare and late-stage vaccine candidates are in development for malaria at GSK and for dengue at Sanofi. Given the scale of the health threat posed by these diseases, we expect these to garner significant attention in the coming year:

- GSK's malaria vaccine Mosquirix (RTS,S) has to date demonstrated sub-optimal efficacy (c.30%) in infants (albeit better efficacy in toddlers) but we await longer-term Phase III results, together with data indicating the effect of a booster. Even if the efficacy levels do not improve upon those reported so far, GSK has committed to price the vaccine on a not-for-profit basis so that affordability is not an impediment (we assume $3/course, at the low end of prices paid by UNICEF) and we believe it could still represent a key weapon in the fight against a disease that is treatable yet kills 1,300 children a day (especially in highly endemic countries such as Nigeria and the Democratic Republic of Congo). GSK filed the vaccine for approval in July 2014 and thus it could become available by the end of 2015, pending a policy recommendation by the WHO. Sales would likely be immaterial in a GSK context, perhaps peaking at $80-130m, and would generate no profit, reflecting the philanthropic nature of the project (which was part funded by the Bill & Melinda Gates Foundation).
- Success in two recently-reported pivotal Phase III trials (one in >20,000 Latin American children/adolescents; the other in >10,000 Asian children) bodes very positively for Sanofi's dengue vaccine (CYD TDV). Headline data shows 56-61% efficacy, together with major public health benefits (reduced hospitalisations and severe cases). This suggests that there is a strong chance of widespread usage of the vaccine in endemic regions. With high levels of demand projected, this could well generate sales approaching €1bn pa within 3-5 years, in our view. Unlike GSK's malaria vaccine this is not considered a philanthropic project by management (although pricing would be tiered for poorer countries) and the vaccine could become a meaningful EPS and revenue driver for Sanofi. The key risk is that the vaccine's weaker ability to protect against one of the four circulating serotypes of dengue (DENV-2) may limit reimbursement coverage in countries with a high relative incidence of this serotype. That said, the vaccine's *overall* efficacy is impressive and virus serotypes fluctuate with time, hence we do not see this as a major impediment to broad adoption. With filings expected in 1Q15 and rapid approvals likely, the first launch could occur in late-2015 with most launches over 2016/17.

Ratings and valuations: European large-cap pharma

Clearly the subject matter in this report has very limited relevance to forecasts for the short-to-medium term financial performance of the European large-cap pharma companies, with the likely exception of Sanofi (due to the sales/earnings sensitivity of its potential dengue vaccine). Instead we view this as more of a discussion in regard to SRI and long-term strategy. Nevertheless, Figure 4 shows valuation metrics for our large-cap coverage stocks.

Figure 4: Ratings, TPs and valuation metrics for European large-cap pharma

Stock	Rec.	Price	Target	Mcap	Mcap	PER				EV/EBITDA	Div yield	FCF yld
		9-Sep-14		(local; bn)	($bn)	2014E	2015E	2016E	2017E	2015E	2015E	2015E
EU major Pharma					**1,051.3**	**18.2**	**17.0**	**15.7**	**14.6**	**12.3**	**3.4%**	**6.8%**
AstraZeneca	Hold	4,572.0p	4,000.0	57.5	92.9	16.4	17.6	16.8	17.3	11.9	3.8%	5.8%
Bayer AG	Buy	EUR 105.6	125.0	87.3	113.1	17.6	15.1	13.2	12.0	11.3	2.5%	5.4%
GlaxoSmithKline	Hold	1,432.5p	1,500.0	68.8	111.2	15.3	14.7	13.6	12.5	13.2	5.6%	12.3%
Novartis	Hold	CHF 87.1	83.0	210.6	226.1	17.8	16.0	15.6	14.8	12.9	3.2%	6.7%
Novo Nordisk	Hold	DKK 258.1	240.0	672.1	116.9	24.9	22.0	19.4	17.4	15.8	2.2%	4.3%
Roche	Buy	CHF 270.9	295.0	229.7	246.6	18.9	18.5	17.0	15.5	11.7	3.1%	6.1%
Sanofi	Buy	EUR 85.8	92.0	111.6	144.4	16.4	14.8	13.5	12.3	9.6	3.7%	7.6%

Source: Deutsche Bank

Socially responsible, long-term business sense

Helping the >2bn pa at high risk of tropical diseases

The provision of drugs and vaccines for tropical diseases is generally thought of as a philanthropic endeavor for the pharmaceutical industry, typified by bulk donations of relatively basic, usually off-patent anti-infectives. However, more aggressive and far-reaching disease management goals from the World Health Organization (WHO; an agency of the United Nations) have resulted in recent years in an intensification of the funding and supply of - and in some cases research and development into - a number of tropical diseases. These include the more common diseases (malaria, TB) as well as 17 specifically-identified 'neglected tropical diseases' (NTDs; dengue, sleeping sickness etc) for which the WHO has global targets to control or eradicate by 2020. 1.2bn globally are at high risk of malaria while around one in three is at risk of NTDs, one in six already has an NTD and 1.4bn of the world's poorest people are affected.

Figure 5: The 17 WHO-defined 'neglected tropical diseases'

Dengue	Cysticercosis/Taeniasis *(tapeworms)*
Rabies	Dracunculiasis *(Guinea worm disease)*
Chagas disease	Echinococcosis
Human African trypanosomiasis *(sleeping sickness)*	Schistosomiasis *(bilharzia)*
Leishmaniasis	Lymphatic filariasis *(elephantiasis)*
Buruli ulcer	Onchocerciasis *(river blindness)*
Leprosy	Soil-transmitted helminthiases *(intestinal worms)*
Trachoma	Food-borne trematodiases
Yaws	

Source: 'Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation' (WHO, 2012), Deutsche Bank

Long-term investment in >40% of the world's population

In our view the pharma industry has a moral and humanitarian imperative to assist in relieving the burden of these diseases. However, it also makes sound business sense on a longer term basis, given that the tropics (comprising 144 nations and territories; see Annex 1) produce around 20% of the world's GDP and are home to more than 40% (2.8bn) of the world's population (the latter proportion is projected to reach 50% by 2050), according to the United Nations. While many of those blighted by tropical diseases are citizens of the world's poorest nations today (the tropics include 43 of the 48 UN-designated Least Developed Countries), economic development in the coming decades is likely to mean these countries will constitute the pharma industry's customers of tomorrow. To this end, many pharma companies routinely provide services and skills that extend well beyond the basic provision of medicines, eg, training doctors and nurses, participating in health education campaigns, improving supply chain logistics (a major issue for distant rural communities), researching and developing new medicines and vaccines on a not-for-profit basis and foregoing/pooling IP protection so that local manufacturers can produce critically needed drugs. We thus see drug company attitudes to the developing world (and in this report tropical diseases specifically) as a key element for any socially-responsible investment (SRI) appraisal as well as a potential leading indicator for longer term commercial success.

Tracking the companies with Access to Medicine Index

While not specifically focused on tropical diseases, the activities of the largest 20 pharmaceutical companies in the developing countries are audited in detail by the Access to Medicine Foundation, a not-for-profit organization (part-funded by the Bill & Melinda Gates Foundation) that aims "to encourage pharmaceutical companies to make their products more available, affordable and accessible for millions of people worldwide who do not have reliable access to medicine". This results in the publication of the biennial Access to Medicine Index which ranks the companies on a number of criteria, including pricing, access, R&D and IP flexibility. The most recent publication was in 2012 and a new version is due in November. While the Access to Medicine Index extends beyond tropical diseases into other common diseases of low- and middle-income countries (eg, respiratory and heart disease), there is clearly considerable overlap and we acknowledge this as a key source.

The most recent (2012) Index (Figure 6) showed the European large-cap companies to be well represented with GSK and Sanofi ranked first and third respectively in their overall access-to-medicines performance and with Novo Nordisk, Novartis, Bayer and Roche also appearing in the top ten. The detailed sub-category breakdown revealed GSK and Sanofi to be the most highly ranked both in terms of their philanthropic activities and in specific R&D towards diseases of the developing world. For those readers who would like to investigate the Index ranking in more detail we would encourage them to access the full report on the www.accesstomedicineindex.org website.

Figure 6: Access to Medicines 2012 top 20 companies by rank (EU large caps shaded; top 5 per category shown in bold)

	Overall ranking	Access to medicines	Public policy	R&D	Pricing, manufacturing & distribution	Patents & licensing	Capability Advancement	Donations & Philanthropic Activities
GlaxoSmithKline	**1**	**1**	**2**	**1**	**2**	**3**	**1**	**1**
Johnson & Johnson	**2**	**2**	**5**	**3**	**3**	**2**	**3**	**3**
Sanofi	**3**	**4**	**1**	**2**	7	10	**2**	**2**
Merck & Co.	**4**	6	8	**4**	8	**4**	8	**5**
Gilead	**5**	7	10	13	**1**	**1**	10	11
Novo Nordisk	6	**3**	**3**	8	**4**	6	**4**	**4**
Novartis	7	8	7	**5**	6	7	7	8
Merck KGaA	8	9	12	6	13	14	**5**	6
Bayer	9	**5**	13	16	12	9	6	9
Roche	10	12	8	10	10	8	9	15
Pfizer	11	13	15	11	9	16	11	7
Bristol-Myers Squibb	12	14	**4**	14	11	11	18	13
AbbVie	13	15	14	15	**5**	15	15	17
Eli Lilly	14	16	6	9	14	13	16	14
Eisai	15	11	11	7	16	17	14	10
AstraZeneca	16	10	19	12	17	12	17	16
Boehringer-Ingelheim	17	17	20	20	15	**5**	12	12
Takeda	18	18	17	17	20	19	13	18
Daiichi Sankyo	19	19	18	18	18	20	20	20
Astellas	20	20	16	19	19	18	19	19

Source: Access to Medicines Index 2012, Deutsche Bank

The following Figure, adapted from the Access to Medicine Index, sets out the exposure of the European large-cap pharma companies to the key tropical diseases, both in terms of marketed products (including vaccines) and of dedicated R&D activity. In total, our coverage companies have 131 marketed products and 54 investigational pipeline products targeting these diseases. The limited exposures of AstraZeneca and Novo Nordisk reflect their therapeutic focus on other disease areas (the strong #6 showing by Novo Nordisk in the Index instead reflects its position as world leader in insulin supply).

Figure 7: European large-cap pharma company exposure to tropical diseases

	AstraZeneca	Bayer	GSK	Novartis	Novo Nordisk	Roche	Sanofi
Marketed products							
Malaria		x		x			x
Dengue		x					
Lymphatic filariasis			x				
Soil transmitted helminthiasis		x					
Leishmaniasis							x
Trypanosomiasis		x					
Schistosomiasis		x					
Trachoma							
Onchocerciasis							
Leprosy				x			
Chagas disease		x					
Yaws							
Fascioliasis				x			
Buruli ulcer							
Dracunculiasis							
Paediatric vaccines			x	x			x
HIV/AIDS			x	x		x	
Tuberculosis				x		x	x
R&D activity							
Malaria		x	x	x			x
Dengue		x	x	x			x
Lymphatic filariasis							
Soil transmitted helminthiasis							
Leishmaniasis			x	x			x
Trypanosomiasis		x	x	x			x
Schistosomiasis		x					
Trachoma				x			
Onchocerciasis							
Leprosy							
Chagas disease		x	x	x			
Yaws							
Fascioliasis							
Buruli ulcer							
Dracunculiasis							
Paediatric vaccines			x	x			x
HIV/AIDS			x	x			x
Tuberculosis	x	x	x	x			x

Source: Access to Medicine Index 2012, Deutsche Bank

In the remainder of this report we discuss each of the key tropical diseases and the efforts made to control these and we also profile the European large-cap companies individually in terms of their exposure to tropical diseases.

Neglected tropical diseases

WHO has marshalled global efforts on 17 diseases

Since its formation in 1946, the World Health Organization (WHO; an agency of the UN) has been actively involved in devising, enacting and supporting public health programs for combating disease in the world's poorest nations. In 2010, it published its first report on neglected tropical diseases (NTDs), setting out specific targets for the eradication of certain diseases (dracunculiasis, by 2015; Yaws, by 2020) and for the elimination (defined as reduction in incidence to zero) and control (defined as reduction in either the incidence, prevalence, intensity, morbidity, mortality or a combination thereof) of the remaining NTDs. As highlighted earlier, one in three people globally are at risk of contracting an NTD and one in six already has an NTD, mostly among the world's poorest nations. Figure 8 and Figure 9 show the full list of 17 NTDs and the WHO's targets for these diseases by 2020.

Figure 8: Neglected Tropical Diseases (classified by pathogen sub-type)

Microscopic pathogens	Macroparasitic pathogens
Virus	**Helminth (worms and flukes)**
Dengue	Cysticercosis/Taeniasis *(tapeworms)*
Rabies	Dracunculiasis *(Guinea worm disease)*
Protozoa (single-celled organisms)	Echinococcosis
Chagas disease	Schistosomiasis *(bilharzia)*
Human African trypanosomiasis *(sleeping sickness)*	Lymphatic filariasis *(elephantiasis)*
Leishmaniasis	Onchocerciasis *(river blindness)*
Bacteria	Soil-transmitted helminthiases *(intestinal worms)*
Buruli ulcer	Food-borne trematodiases
Leprosy	
Trachoma	
Yaws	

Source: 'Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation' (WHO, 2012), Deutsche Bank

Figure 9: WHO targets for NTDs in 2020

2020 target	Disease
Eradication	Dracunculiasis (*Guinea worm disease*; eradication by 2015); Yaws
Global elimination	Blinding trachoma; leprosy; Human African trypanosomiasi (*sleeping sickness*); lymphatic filariasis (*elephantiasis*)
Regional/country elimination	Rabies; Chagas disease; visceral leishmaniasis; schistosomiasis (*bilharzia*); onchocerciasis (*river blindness*)
Intensified control	Dengue; Buruli ulcer; cutaneous leishmaniasis; cysticercosis/taeniasis; echinococcosis; foodborne trematodiases; soil-transmitted heminthiases (*intestinal worms*)

Source: 'Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation' (WHO, 2012), Deutsche Bank

The London declaration on NTDs

This marshalling of resources on a specific group of diseases was followed by the WHO's publication of a roadmap, in January 2012, setting out specific annual targets for the achievement of these goals ('*Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation*'). Publication of this roadmap became the platform for the signing of the London declaration on Neglected Tropical Diseases by 22 companies and stakeholders (Figure 10). Pharmaceutical/medical company signatories included Abbott (now AbbVie), AstraZeneca, Bayer, Becton Dickinson, Bristol-Myers Squibb, Eisai, Gilead, GlaxoSmithKline (GSK), Johnson & Johnson, Merck KGaA, Merck, Novartis, Pfizer and Sanofi. Non-corporate

and philanthropic signatories included the Bill & Melinda Gates Foundation, CIFF (Childrens Investment Fund Foundation), DFID (UK Department for International Development), DNDi (the R&D organization, Drugs for Neglected Diseases initiative), Lions Clubs International, Mundo Sano, USAID (US Agency for International Development) and the World Bank.

Figure 10: The London declaration on Neglected Tropical Diseases (January 2012)

For decades, partners including pharmaceutical companies, donors, endemic countries and non-government organisations have contributed technical knowledge, drugs, research, funding and other resources to treat and prevent Neglected Tropical Diseases (NTDs) among the world's poorest populations. Great progress has been made, and we are committed to build on these efforts.

Inspired by the World Health Organization's 2020 Roadmap on NTDs, we believe there is a tremendous opportunity to control or eliminate at least 10 of these devastating diseases by the end of the decade. But no one company, organization or government can do it alone. With the right commitment, coordination and collaboration, the public and private sectors will work together to enable the more than a billion people suffering from NTDs to lead healthier and more productive lives – helping the world's poorest build self-sufficiency. As partners, with our varied skills and contributions, we commit to doing our part to:

- Sustain, expand and extend programmes that ensure the necessary supply of drugs and other interventions to help eradicate Guinea worm disease, and help eliminate by 2020 lymphatic filariasis, leprosy, sleeping sickness (human African trypanosomiasis) and blinding trachoma.
- Sustain, expand and extend drug access programmes to ensure the necessary supply of drugs and other interventions to help control by 2020 schistosomiasis, soil-transmitted helminthes, Chagas disease, visceral leishmaniasis and river blindness (onchocerciasis).
- Advance R&D through partnerships and provision of funding to find next generation treatments and interventions for neglected diseases.
- Enhance collaboration and coordination on NTDs at national and international levels through public and private multilateral organisations to work more efficiently and effectively together.
- Enable adequate funding with endemic countries to implement NTD programmes necessary to achieve these goals, supported by strong and committed health systems at the national level.
- Provide technical support, tools and resources to support NTD-endemic countries to evaluate and monitor NTD programmes.
- Provide regular updates on the progress in reaching the 2020 goals and identify remaining gaps.

To achieve this ambitious 2020 vision, we call on all endemic countries and the international community to join us in the above commitments to provide the resources necessary across sectors to remove the primary risk factors for NTDs—poverty and exposure—by ensuring access to clean water and basic sanitation, improved living conditions, vector control, health education, and stronger health systems in endemic areas.

We believe that, working together, we can meet our goals by 2020 and chart a new course toward health and sustainability among the world's poorest communities to a stronger, healthier future.

Source: WHO press release

In addition to announcing $785m in new funding to support R&D efforts and drug distribution (including $363m from the Gates Foundation), the declaration included specific commitments from the pharmaceutical companies involved. These included the expansion of drug donations to an average of 1.4bn treatments pa and the signing of new collaborative agreements in R&D and compound library access with the DNDi (including contributing to the WIPO Re:Search database of research compounds). These R&D agreements are targeted to generate new drugs for NTDs including river blindness, lymphatic filariasis, sleeping sickness, Chagas disease and visceral leishmaniasis.

Progress to date

Subsequently, in 2013, the WHO published a second report on NTDs ('*Sustaining the drive to overcome the global impact of neglected tropical diseases*') which updated on the progress made to date and which we use as a key source in the following pages of this report. Amongst other things this highlighted the significant increase in donated medicines since 2012, including drugs for helminth (worm) infections (albendazole, from GSK; mebendazole, Johnson & Johnson; praziquantel, Merck KGaA) and the "impressive progress" made towards eradicating the potentially disfiguring bacterial disease Yaws.

A survey by G-FINDER (Global Funding of Innovation for Neglected Diseases) showed that 2012 did indeed mark a year of increased investment in NTDs with dedicated R&D funding rising by 3% to $3.2bn – reversing several years

of decline. Within this, two-thirds of funding ($2.0bn, +1.5%) was provided by the public sector (notably the US, UK and EC), with the balance divided between philanthropic bodies ($631m, +9.4%; notably the Bill & Melinda Gates Foundation and Wellcome Trust) and the pharma industry ($527m, +2.5%).

Most recently (on 2 April 2014), an additional $240m in external funding was announced to support the WHO's efforts on NTDs. Key sources of this new injection of funds include the Bill & Melinda Gates Foundation, the Children's Investment Fund Foundation and the World Bank. Of this, $120m is specifically targeted at further collaboration "*to combat soil-transmitted helminths, a group of intestinal worms that are among the most common infections in children living in poverty"* with the other $120m committed to "*support the fight against neglected diseases, including support for school-based deworming programmes* (source: Reuters). The press release noted that "*the new money follows a pledge by 13 drugmakers two years ago to donate medicines to tackle 10 parasitic and bacterial infections - such as river blindness, Guinea worm and sleeping sickness - that threaten one in six people worldwide".*

Pharmaceutical company donations for NTDs

Figure 11 shows the drug donations made by the pharmaceutical industry to date. As can be seen, among the European large-cap companies, Bayer, GlaxoSmithKline, Novartis and Sanofi have each contributed substantially, helping the WHO in its fight against sleeping sickness (human African trypanosomiasis), worm infections (lymphatic filariasis, heminthiases), fluke infections (fascioliasis, paragonimiasis) and leprosy.

Figure 11: Drug donations for Neglected Tropical Diseases

Company	Drug	Donation
Large-cap Europeans:		
Bayer	Nifurtimox	Up to 400,000 tablets pa over 2009-14 for human African trypanosomiasis (HAT; sleeping sickness); up to 1 million tablets pa over 2012-2017 for second-line treatment of Chagas disease (this annual amount was doubled under the London declaration)
	Suramin	Up to 10,000 vials pa until November 2012 for HAT
GlaxoSmithKline	Albendazole	600m tablets pa supplied for as long as needed for lymphatic filariasis and 400m tablets pa supplied to 2020 for soil-transmitted helminthiases (extended under the London declaration)
Novartis	Multidrug therapy (rifampicin, clofamazine and dapsone in blister packs); loose tablets of clofamazine	Unlimited supply for as long as needed for leprosy and its complications (this was extended under the London declaration)
	Triclabendazole	Up to 600,000 tablets pa for fascioliasis and paragonimiasis
Sanofi	Eflornithine	Unlimited quantity until 2020 for HAT (extended under London declaration)
	Melarsoprol	Unlimited quantity until 2020 for HAT (extended under London declaration)
	Pentamidine	Unlimited quantity until 2020 for HAT (extended under London declaration)
	Notezine (diethylcarbamazine)	120 million tablets for lymphatic filariasis with support from Eisai and the Bill & Melinda Gates Foundation for 2012-13 (with Eisai to supply from 2014 so supply is assured to 2020)
Other companies:		
Eisai	Diethylcarbamazine	Up to 2.2 billion tablets until 2020 for lymphatic filariasis
Gilead	AmBisome	Up to 445,000 vials over 2012-17 for visceral leishmaniasis in S.E Asia and East Africa
Johnson & Johnson	Mebendazole	Up to 200 million tablets pa until 2020 for soil-transmitted helminthiases control programs for school-age children
Merck & Co.	Ivermectin	Unlimited supply for as long as needed for lymphatic filariasis and onchocerciasis
Merck KGaA	Praziquantel	Up to 250m tablets pa for unlimited period for schistosomiasis (expanded ten-fold, from 25m tablets pa previously, under the London declaration)
Pfizer	Azithromycin	Unlimited quantity until at least 2020 for blinding trachoma

Note: all donations made through the WHO except ivermectin donation made directly by Merck & Co..
Source: 'Sustaining the drive to overcome the global impact of neglected tropical diseases' (WHO, 2013), company data, Deutsche Bank

Profiles of the 17 NTDs

We outline next each of the 17 NTDs, the strategies being employed to eradicate, eliminate or control them and progress towards the WHO's targets. Following this we specifically address the highest incidence NTD, dengue fever, which by some estimates has overtaken malaria as the most common tropical disease and for which a potentially ground-breaking vaccine is in late-stage development by Sanofi (with two successful pivotal Phase III trials now reported). We also provide an update on malaria, for which global mortality has declined by c.40% due to effective treatment and prevention strategies and yet which still results in the death of 1,300 children per day, mostly in sub-Saharan Africa. New drug treatments are in development for malaria (which is important due to growing treatment resistance) together with the first ever vaccine from GlaxoSmithKline (which could reach the market in 2015).

Dengue

Figure 12: Dengue overview

Cause	Dengue (also known as dengue fever) results from infection by a type of flavivirus (dengue virus). The disease is mainly transmitted by the bite of female mosquitos of the species *Aedes aegypti*, although transmission can also occur through blood transfusion and organ transplantation from infected donors. The dengue virus exists in four principal strains or serotypes (referred to as DENV-1, DENV-2, DENV-3 and DENV-4). Recent work in Thailand (announced in October 2013) suggests that a fifth serotype may also have arisen, although we note that the genetic variation in dengue viruses tends to be region-specific (ie, this putative new variant may not be present on a global basis).
Clinical manifestations	Initial infection results in an incubation period that is generally less than one week (maximum two weeks) before symptoms typically occur. For many the symptoms are mild (eg, slight fever) and the majority (80%) remain essentially symptom-free due to natural immunity. However, some patients develop a severe flu-like illness (with high fever, arthralgia, headache etc) and a measles-like skin rash. Furthermore a small proportion can develop a potentially fatal complication known as severe dengue (previously: dengue haemorrhagic fever) which involves internal bleeding and shock.
Affected regions	The WHO estimates that the incidence of dengue has increased by >30x in the last 50 years and the disease now represents a major global health threat. It is generally thought that the number of infections per annum has reached 50-100m in the >125 affected endemic countries (this compares with just 3 countries in 1955 and 8 in 1959). However, a recent publication in the journal *Nature* (Apr 25, 2013; 496(7446): 504–507) puts the number of annual infections far higher, at 390m. Given the expanded geographic reach, around half the global population is now theoretically at risk of infection, principally in LatAm, Africa, S.E Asia and the Western Pacific. Member states of the WHO reported around 4,200 deaths from dengue and over 2m cases of disease in 2010/11, both more than double the figure of five years earlier and both almost certainly massively under-reported (due to a combination of under-diagnosis in remote regions and misdiagnosis of dengue as other fever-bearing tropical diseases, notably malaria). Severe dengue is now a key cause of hospitalisation in Asia and LatAm.
Treatment	There are no specific medications for dengue and anti-viral approaches are still in an early research phase. Treatment therefore centres on supportive care (eg, rehydration, symptom alleviation and blood transfusion in more severe cases). The launch of an effective vaccine is a high priority, of which the most advanced is in development at Sanofi – this seeks to protect against the four main serotypes and has reported positive results from two pivotal Phase III trials. Mosquito control via insecticidal spraying, bednets and removing their natural breeding habitat (standing water sources) is a key component of disease control.
Progress to date	The WHO's *Global strategy for dengue prevention and control, 2010-2020* seeks to cut mortality and morbidity from the disease by 50% and >25% respectively and is based on a number of key elements. These include, amongst others, improved diagnosis and surveillance (including monitoring pandemic outbreaks), sustainable vector (ie, mosquito) control, and (once available) the implementation of vaccination. With no effective vaccine currently available (this is likely to change if, as we expect, the Sanofi vaccine becomes available in the 2015+ timeframe), current efforts focus more on prevention of transmission. The fact that *A. aegypti* was largely eradicated in the Americas by the early 1970s but has since resurged, with an accompanying rise in the number of dengue cases to a hyperendemic state, highlights the high importance of vector control.
WHO target	The WHO aims to have sustainable dengue vector control interventions established in 10 endemic priority countries by 2015. By 2020 it targets having dengue control and surveillance systems established in all regions and reductions in the number of dengue cases and deaths of >25% and 50% respectively (as compared with 2010).

Source: WHO website, Nature, miscellaneous medical websites, company data, Deutsche Bank

Rabies

Figure 13: Rabies overview

Cause	Rabies is a disease that is caused by viruses of the *lyssavirus* family (rabies virus, bat lyssavirus) and is transmitted by saliva from the bite of infected animals. Most animals (domestic or wild) can act as hosts for the virus but those posing the most threat to humans include dogs, cats, wolves, foxes, monkeys and bats. Animals infected with the rabies virus tend to be highly aggressive and exhibit unusual behavior patterns, resulting from the virus having penetrated their nervous system.
Clinical manifestations	Initial infection is symptom-free but during this phase (which can last from two weeks up to three months) the virus penetrates the nerves and travels to the central nervous system. Serious symptoms then follow including mental confusion, paralysis and hydrophobia (the characteristic fear of water). Death usually occurs within 1-2 weeks of symptoms first appearing. As discussed below, post-exposure prophylaxis before symptoms occur has been highly successful in reducing deaths.
Affected regions	Rabies is present in 150 countries around the world in virtually all continents. Up to 3bn people are estimated to be at risk in poor rural areas of Africa and Asia where access to post-exposure prophylaxis (human vaccines, immunoglobulin) is either inadequate or non-existent. Among these populations, some 60,000 people die per year, of which 40% are children. In the past decade, China and India accounted for 25-40% of global deaths from rabies, according to the WHO.
Treatment	Post-exposure prophylaxis (within 10 days of the animal bite) with rabies vaccine and human rabies immunoglobulin is completely successful in preventing the onset and worsening of serious disease. Novartis (Rabipur, Rabavert) and Sanofi (Verorab) are key suppliers of vaccines. In addition, management of animal populations (by mass vaccination of dogs with rabies vaccine and curbing dog breeding) is employed to substantially lower the threat of transmission. The WHO promotes a lower volume/cost intradermal vaccine for pre- and post-exposure prophylaxis.
Progress to date	The combined vaccination strategies for humans and dogs outlined above have resulted in the near elimination of dog rabies in North America, Europe and parts of Asia and LatAm. Furthermore the number of rabies deaths in China has declined from a peak of over 3,000 in 2007 to less than 2,000 recently, while some parts of India have seen deaths fall to zero. Dog rabies, however, remains a particular problem in Africa, due to the paucity of large-scale dog vaccination programs. Furthermore, the transmission of rabies by vampire bats in the more remote rural parts of LatAm (eg, the Amazon region) is a growing problem.
WHO target	The WHO aims to have eliminated rabies in LatAm by 2015 and in S.E Asia and the Western Pacific regions by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Chagas disease (American trypanosomiasis)

Figure 14: Chagas disease overview

Cause	American trypanosomiasis, better known as Chagas disease, results from infection by the protozoan parasite *Trypanosoma cruzi* and is mainly transmitted by triatomine bugs (aka kissing bugs). These blood-sucking insects bite and deposit their contaminated faeces, allowing the bacteria harboured therein to pass through skin membranes to infect humans. The disease is also spread by other means, including organ transplantation, blood transfusion and eating contaminated food.
Clinical manifestations	Initial infection is followed by an acute phase which lasts up to three months and is often either symptom-free or has symptoms which closely resemble those of other diseases (eg, fever, diarrhea, joint pain and rash). A characteristic symptom, however, is Romana's sign – a swelling of the eyelid (from infection by the insect faeces near the bite or inadvertent rubbing of the faeces into the eye). The subsequent chronic phase lasts many years and involves the parasites entering various target organs. In most cases, individuals remain symptom-free despite life-long infection but in 20-40% of cases, the parasites have entered heart muscle or the digestive tract and serious life-threatening problems can arise (heart failure, colon enlargement). Since the 1980s, co-infection with HIV has become an increasing problem.
Affected regions	The vast majority of the estimated 7-8m infected people worldwide inhabit 21 LatAm countries. Mexico, Brazil and Argentina are estimated to have the highest number of cases. Those outside of LatAm principally arise from population migration. As discussed above, most of those infected are symptom-free and unaware of their disease.
Treatment	Anti-microbial treatment is available in the form of nifurtimox (donated by Bayer) and benznidazole (produced by the Brazilian company Laboratorio Farmaceutico do Estado de Pernambuco or LAFEPE, following a technology transfer from Roche in 2008). Vector and transmission control is the WHO's primary focus (see below).
Progress to date	The WHO has a two-part strategy for Chagas disease which involves interrupting transmission (through for example improved blood screening, insecticidal spraying of households, use of bednets and improved food hygiene) and providing patient care (via medication and support programs). Unlike most other neglected tropical diseases, little information is available on whether these efforts have yielded progress towards the WHO's disease control and elimination targets.
WHO target	The WHO aims to have interrupted regional transmission through blood transfusion by 2015 and to have interrupted intra-domiciliary (ie, household) transmission in the Americas by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Human African trypanosomiasis (sleeping sickness)

Figure 15: Human African trypanosomiasis overview

Cause	Human African trypanosomiasis, colloquially known as sleeping sickness, results from infection by the protozoan parasite *Trypanosoma* and is transmitted by the bite of the tsetse fly (species: *Glossina*). The most common (chronic) form of the disease (98% of cases) is caused by *T. brucei gambiense*, usually found in Western/Central Africa, while the much less prevalent acute form is caused by *T. brucei rhodesiense* and mainly confined to Eastern/Southern Africa.
Clinical manifestations	Initial infection is followed by immune-mediated flu-like symptoms (fever, arthralgia, headache etc). After a period of time, which may be weeks or months depending on the type of trypanosomal bacterium, the disease enters a second, more severe (neurological) stage as the parasites cross the blood-brain barrier and invade the central nervous system. The initial warning sign is disturbed sleep cycles (hence the nickname for the disease), followed by progressive physical and mental deterioration. This in turn leads ultimately to coma and organ failure. The disease is invariably fatal unless detected and treated promptly.
Affected regions	The chronic form of Human African trypanosomiasisiasis (*gambiense*) is endemic in 24 African countries while the acute form (*rhodesiense*) is endemic in 13 countries. Since 2009, less than 10,000 new cases pa have been reported, a dramatic reduction from the estimated 300,000 cases in 1995. Estimates, however, suggest there is significant under-reporting and that the real number of cases may be around double those reported. In total some 70m people are at risk of disease in sub-Saharan Africa.
Treatment	Historically, anti-microbial treatment was given with melarsoprol but, while effective at killing the trypanosome parasites, this was associated with unacceptable toxicity (it is chemically related to the poison arsenic). The WHO has, since 2007, supplied kits comprising the much safer combination of nifurtimox and eflornithine (donated by Bayer and Sanofi, respectively). Two alternative anti-protozoal drugs are also supplied by Bayer (suramin) and Sanofi (pentamidine) via donation to the WHO.
Progress to date	The WHO supplies treatment kits (based on the improved medications outlined above) and training for healthcare workers. It also supports increased efforts at early diagnosis (principally by microscopic examination of bodily fluids, eg, blood, lymph or cerebrospinal fluid). In 2012, as part of its roadmap, the WHO established elimination criteria for the disease and surveillance targets. By 2015 it expects to have reduced the number of new cases reported annually to 4,500 and, by 2020, to have cut this to below 2,000 with the disease eliminated in >90% of affected regions.
WHO target	The WHO aims to have eliminated the disease globally by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Leishmaniasis

Figure 16: Leishmaniasis overview

Cause	The leishmaniases are a group of infections caused by different species of the protozoan parasite *Leishmania*. Transmission occurs via the bite of infected female sandflies.
Clinical manifestations	Different forms of the disease include: cutaneous leishmaniasis (the most prevalent and benign, associated with self-resolving ulcers); visceral leishmaniasis or kala-azar (in which the parasites migrate to vital organs, including the liver and spleen, leading to fever, weight loss and anaemia and is generally fatal if not treated); and mucocutaneous leishmaniasis (which involves severe destruction of soft tissue in the mouth, nose and throat and can be highly disfiguring).
Affected regions	Leishmaniasis is present in 98 countries and across five continents. There are around 1.3m new cases per annum, the majority of which are the non life-threatening cutaneous form. However, the WHO reports that there are 300,000 cases pa of visceral leishmaniasis, which are in turn associated with over 20,000 deaths. Six countries report the vast majority of cases of visceral leishmaniasis (Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan) placing around 310m people at risk of infection. Unlike a number of other neglected tropical diseases, the number of cases is increasing as a consequence of population movement. Some sources suggest that this is the second-biggest source of death globally from parasitic infection (after malaria).
Treatment	Injected liposomal amphotericin B (AmBisome, donated by Gilead) is the recommended treatment for visceral leishmaniasis and is the principal regimen in the Indian sub-continent. In East Africa, a different anti-microbial combination (sodium stibogluconate and paromomycin) is incorporated in national guidelines. Mucocutaneous disease may also require corrective surgery. Control of sandlfies via insecticides and treated bed nets is also part of a concerted disease control strategy.
Progress to date	The WHO established guidelines for controlling leishmaniasis in 2010, encompassing medicinal treatment together with disease detection and surveillance. By 2015 it aims to have detected and treated all cases of visceral leishmaniasis in the Indian sub-continent and to have detected and managed the vast majority (>70%) of cases in other key endemic regions.
WHO target	The WHO aims to have eliminated visceral leishmaniasis from the Indian sub-continent by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Buruli ulcer

Figure 17: Buruli ulcer overview

Cause	Infection due to the bacterium *Mycobacterium ulcerans (*which is related to the bacterium that causes leprosy; see below). The basis of transmission has not been ascertained although it has been suggested that contaminated water may be involved.
Clinical manifestations	Initial infection results in a painless nodule on the skin – often on the limbs - but the subsequent release of bacterial toxins results in tissue necrosis (death). The resulting ulcer can become very large and painful with extensive tissue destruction. This in turn can cause disfigurement, a reduction in mobility and encourage serious secondary infections (sepsis, tetanus).
Affected regions	33 countries have reported cases of buruli ulcer across a number of regions/continents, mostly in Africa. An increased incidence has been reported in Gabon, Ghana and Australia but it is likely that there is under-reporting globally of this condition due to limited knowledge. The total number of new cases averaged around 5,000 pa over 2005-2011.
Treatment	Treatment with antibiotic therapy (rifampicin plus streptomycin) has been the WHO recommended course of action since 2004. An oral antibiotic regimen is also under study by the WHO (see below). In cases of severe ulceration, hospitalisation and surgery is required to remove necrotic tissue and to correct the resulting skin deformities.
Progress to date	The Global Buruli Ulcer Initiative (GBUI) was set up in 1998 and includes the WHO and a number of governmental and academic partners. The WHO estimates that around 40,000 have received antibiotic therapy since its recommendation in 2004, halving the number of cases of surgery. By 2015, the WHO aims to have completed a clinical study of an all-oral antibiotic combination (rifampicin plus clarithromycin) which, assuming it is successful, will increase access to effective medication.
WHO target	The WHO aims to have 70% of all cases detected and cured early with antibiotics in all endemic countries by 2020.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Leprosy

Figure 18: Leprosy overview

Cause	Infection due to the bacterium *Mycobacterium leprae*. Transmission is thought to be primarily via contact with nasal droplets (and possibly blood) from infected individuals. Most people (95%) have natural immunity to the bacterium.
Clinical manifestations	Characteristic disfiguring skin lesions (nodules, thickened/pigmented skin patches) are the most visible symptoms of leprosy, traditionally leading to social stigma, isolation and increased poverty levels. However, the disease is also associated with nerve damage (affecting around one-third of those infected), muscle weakness, vision impairment and respiratory problems.
Affected regions	More than 100 countries reported cases of leprosy by the start of 2012. Affected regions included Africa, LatAm, and S.E Asia with smaller numbers of cases arising in the Eastern Mediterranean and Western Pacific. Of the 224,000 new cases reported in 2011, just over half were in India.
Treatment	Treatment with multidrug therapy or MDT, comprised rifampicin, clofazimine and dapsone (donated in unlimited quantities by Novartis) is highly effective. In some cases a simpler regimen of dapsone and rifampicin is sufficient. Vaccination with the BCG vaccine may also offer protection (some studies suggest it is up to 60% effective although controlled trials put this at 26-41%).
Progress to date	The absolute number of leprosy cases has dramatically reduced since the 1960s. Around 200,000-250,000 new cases per year were reported between 2007-2012, down from over 400,000 in 2004. As part of its roadmap to eliminating leprosy globally by 2020, the WHO aims to reduce the global rate of new cases by at least 35% by 2015 as compared with 2010. Its strategy is based on health education and awareness campaigns, improving diagnosis, providing MDT to all endemic regions and encouraging support programs for affected individuals (aimed at reducing stigma and discrimination).
WHO target	The WHO aims to have eliminated leprosy globally by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Trachoma

Figure 19: Trachoma overview

Cause	Eye infection due to the bacterium *Chlamydia trachomatis*. Transmission is via contact with eye discharge from infected individuals (eg, through shared towels, rubbing eyes and touching others, and through flies landing on faces).
Clinical manifestations	Chronic, repeated infection can cause the eyelids and lashes to grow abnormally inwards so that the eyelashes rub against the surface of the eyeball, producing corneal scarring (trichiasis) and severe pain. Ultimately this can lead to blindness. Children are particularly prey to infections along with their mothers (due to exposure to children; adult males are less commonly affected).
Affected regions	Blinding trachoma is found in over 50 countries, usually in very poor rural areas. Although highly endemic in Asia, LatAm, Australia and S.E Asia, the vast majority (85%) of cases are in Africa. In total 325m people live in affected regions, of which over 21m have active trachoma, 7m require surgery to correct trichiasis and over 1m have become blind.
Treatment	Treatment with azithromycin (donated in unlimited quantities by Pfizer) is recommended, in most cases together with tetracycline eye ointment. Surgery is needed for those with trichiasis. These form two key elements of the WHO's SAFE strategy (Surgery, Antibiotics, Facial cleanliness, Environmental improvements).
Progress to date	The WHO determined in 1998 that it would aim to eliminate blinding trachoma by 2020 using the SAFE strategy outlined above. In 2011, over 50m people were treated for trachoma with antibiotic-based therapy. A number of countries (eg, Gambia, Oman, Morocco) have already eliminated the disease and most affected countries have target dates for meeting this goal.
WHO target	The WHO aims to have eliminated blinding trachoma globally by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Yaws (endemic treponematoses)

Figure 20: Endemic treponematoses overview

Cause	Chronic bacterial skin infections caused by various members of the treponeme family. The most common type is Yaws (caused by *Treponema palidum*, sub-species *Pertenue*). Others include endemic syphilis (aka bejel) and pinta. Transmission is via contact with an infected individual and the disease only occurs in humans. Three-quarters of Yaws cases arise in children.
Clinical manifestations	Infection causes a skin lesion (ulcer) at the point of bacterial entry and these multiply across the body if untreated. The face and legs are typically affected. Long-term ulceration can cause disfigurement and serious secondary infections (eg, tetanus).
Affected regions	Yaws is endemic in most humid tropical regions, including LatAm, Asia, Africa and S.E Asia. Endemic syphilis on the other hand is only found in one region in Africa (Sahel) and the Arab peninsula while pinta is confined purely to LatAm.
Treatment	A single oral dose of azithromycin or, if unavailable/inappropriate, an injection of a long-acting penicillin (benzathine benzylpenicillin) can eradicate Yaws infection. Public health education (improved sanitation etc) is also employed.
Progress to date	Mass campaigns by the WHO and UNICEF reduced the prevalence of treponematose disease from 50m to 2.5m between 1952-64 but a resurgence in cases of infection was seen in the 1970s. The WHO recently re-doubled its efforts in 2012 when (as above) it was found that a single dose of azithromycin could effectively eradicate Yaws infection.
WHO target	The WHO aims to have eradicated Yaws globally by 2020.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Cysticercosis/Taeniasis

Figure 21: Cysticercosis/Taeniasis overview

Cause	Infection with the tapeworm (species: *Taenia solium*) as a result of eating infected pork.
Clinical manifestations	Infestation of the intestine by the adult tapeworm (taeniasis) affects nutritional uptake but is of little health consequence. However, if the eggs are ingested and larvae develop in the tissues, a potentially serious disease (cysticercosis) develops. The latter may affect the muscle, skin, eyes and central nervous system. The most severe form, neurocysticercosis, is a common cause of epilepsy in endemic regions (with around a third of epilepsy cases being attributable to this disease) and can be fatal.
Affected regions	Endemic regions encompass most of the developing world, including LatAm, Asia and sub-Saharan Africa. The latter, however, features a number of countries with especially high prevalence (eg, Congo, Mozambique, Senegal, Tanzania, Zambia, S.Africa).
Treatment	Although broad-spectrum anti-helminth drugs (eg, albendazole, praziquantel) can be used to treat *T. solium* infection, the WHO has not yet defined a treatment strategy for the endemic developing regions (see below). Improved de-infestation, sanitation and slaughterhouse conditions for pigs are also likely to form part of any public health strategy
Progress to date	The WHO added cysticercosis, neurocysticercosis and taeniasis to the list of NTDs as recently as 2010. Pilot studies are underway to best define treatment strategies and public-health strategies for preventing transmission (eg, treating pigs with vaccines and the anti-infective oxfendazole).
WHO target	The WHO aims to have a validated strategy available for control of *T. solium* taeniasis/cysticercosis by 2015 and interventions scaled up in certain endemic countries by 2020.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Dracunculiasis (Guinea worm disease)

Figure 22: Dracunculiasis overview

Cause	Infection with nematodes (species: *Dracunculus medinensis*), commonly called the guinea worm, in drinking water.
Clinical manifestations	Infestation affects mobility as adult worms emerge from lower limbs, causing inflammation and burning pains. One study suggested that farmers in Nigeria could be incapacitated for up to 5 weeks.
Affected regions	Effective eradication in many countries has left only four affected (South Sudan, Chad, Mali, Ethiopia). This compares with 20 endemic countries in the 1980s.
Treatment	While there are no effective medicines or vaccines for dracunculiasis, public health measures have been very successful in eradicating the disease in most countries. These measures mainly centre on improving water quality, filtration and sanitation.
Progress to date	With most previously endemic countries now free of disease, the WHO targets the few remaining countries, although displacement of the population in Southern Sudan due to political instability has presented challenges.
WHO target	The WHO aims to have eradicated the disease by 2015.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Echinococcosis

Figure 23: Echinococcosis overview

Cause	Infection with tapeworms (species: *Echinococcus granulosus and E. multilocularis*) from accidental ingestion of eggs carried in faeces of dogs, fixes and carnivores which are the primary host organisms (farm animals are also intermediate hosts).
Clinical manifestations	Infection with *E. granulosus* results in the formation of fluid-filled encapsulated cysts (hydatid cysts), usually in the liver but also in other organs/tissues (eg, kidneys, bone, behind the eye), which in turn cause morbidity via pressure on surrounding tissues and organs. Infection with *E. multilocularis* causes tumours with multiple vesicles, again normally in the liver.
Affected regions	Many countries are affected across multiple regions, although particularly high incidence is found in Northern Africa, the southern part of LatAm, central Asia and parts of Southern and Eastern Europe. The WHO estimates that more than 1m are affected. Infection of livestock, resulting in reduced meat and milk quality, also causes huge economic losses.
Treatment	Fully defined treatment strategies are still in development by the WHO. At present, options include surgery, aspiration of cysts (known as PAIR), anti-infective medicines or watch-and-wait (as the disease can be very slow to develop). Vector control is also important, including treating dogs with anti-infectives, destruction of contaminated meat, and public health education.
Progress to date	The WHO has pilot projects underway to establish treatment and prevention strategies in 2018.
WHO target	The WHO aims to have achieved validated treatment strategies and scale-up in selected countries by 2020.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Schistosomiasis (bilharzia)

Figure 24: Schistosomiasis overview

Cause	Infection with blood flukes (genus: *Schistosoma*) from contaminated fresh water (usually where sanitation is inadequate). Snails act as hosts, passing larvae (cercariae) into the water.
Clinical manifestations	Adult worms live in the veins which drain the human urogenital tract and intestines. Chronic damage is typically caused by the inflammatory immune reaction to eggs which become trapped in bodily tissues and organs. This can result in a variety of symptoms including anaemia, malnutrition, abdominal pain, liver and bladder damage, and increased risk of cancer and HIV.
Affected regions	52 countries still report cases but the vast majority (90%) of infected people live in Sub-Saharan Africa. Also found in Asia and some LatAm countries. Globally 237m at-risk people require preventative disease control and >700m live in endemic regions.
Treatment	The antiparasitic drug praziquantel (donated by Merck KgaA) is used to successfully treat schistosomiasis. Can also be safely used in conjunction with albendazole and/or ivermectin in populations at risk from a wide range of helminthic parasites (lymphatic filariasis, onchocerciasis and soil transmitted helminthiasis). Additional strategies include hygiene education, improving fresh water sanitation and snail control.
Progress to date	The WHO has used praziquantel for preventative control since 2006 (although the drug has been use in schistosomiasis since 1984). Progress appears to have been made as 78 countries previously reported cases of which 19 have recently reported no cases and 7 are still to be determined. WHO projections suggest that the number of people to be treated with praziquantel will peak in 2018 at 235m (requiring 645m tablets).
WHO target	The WHO aims for there to be at least 75% national coverage of all countries requiring preventive treatment by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Lymphatic filariasis (elephantiasis)

Figure 25: Lymphatic filariasis overview

Cause	Infection with filarial nematodes (roundworms; three species: *Wuchereria Bancrofti [90% of cases], Brugia malayi, Brugia timori*) arising from mosquito bites. Commonly contracted in childhood, symptoms are often not fully apparent until adulthood.
Clinical manifestations	Adult worms enter and propagate in the lymphatic system, causing damage to the immune system which can be symptom-free, especially in children and adolescents. However, the associated chronic immune damage can prompt tissue swelling (lymphoedema), hydrocele (genital swelling) and characteristic disfiguring skin and tissue thickening, known as elephantiasis. These serious symptoms frequently affect self-esteem and social standing and result in increased poverty levels.
Affected regions	The WHO estimates that 1.4bn globally in >70 countries require preventative treatment and that 40m people are living with the serious incapacitating symptoms outlined above (25m with genital swelling and 15m with lymphoedema). Roughly two-thirds of exposed individuals live in S.E Asia and around 30% in Africa. The remainder inhabit certain LatAm and Oceania countries.
Treatment	Combination treatment with two antiparasitic drugs is recommended (dosing is 1x pa for 4-6 years for an entire at-risk population, termed mass drug administration or MDA by the WHO). The two choices are albendazole (donated in unlimited quantities by GSK via WHO) plus diethylcarbamazine (donated by Eisai and Sanofi) or, where onchocerciasis (roundworm-mediated River blindness; see below) is also a risk, albendazole plus ivermectin (donated by Merck). Surgery for hydrocele and patient support strategies (medical, financial, emotional) are also important for those with serious symptoms.
Progress to date	The WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000. This aimed to eliminate the disease by 2020 and this target was reconfirmed in 2012. By the latter date, 56 countries (of the >70 where the disease is endemic) had implemented MDA and some 4.4bn treatments had been delivered to nearly 1bn at-risk individuals. The WHO estimates that transmission of lymphatic filariasis has dropped by more than 40% since the GPELF was initiated.
WHO target	The WHO aims to have eliminated the disease globally by 2020 (with 70% of countries certified as free of disease and 30% undergoing post-treatment surveillance). To meet this, it targets that all endemic countries will have achieved MDA by 2015.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Onchocerciasis (River blindness)

Figure 26: Onchocerciasis overview

Cause	Infection with filarial nematodes (roundworms; species: *Onchocerca volvulus*) arising from the bite of infected black sandflies. The latter breed in fast-flowing rivers and streams.
Clinical manifestations	Adult worms produce larvae which migrate to the skin, eyes and organs. This can result in severe itching, disfiguring skin lesions and nodules, visual impairment and blindness.
Affected regions	Over 99% of infected people live in Sub-Saharan Africa. Also found in Yemen and six countries in LatAm.
Treatment	The antiparasitic drug ivermectin (donated in unlimited quantities by Merck) is used to successfully treat onchocerciasis (recommended dosing is at least 1x pa for 10-15 years). Other key strategy is insecticidal spraying (to control blackfly larvae).
Progress to date	The Onchocerciasis Control Project (OCP) brought the disease under control in West Africa between 1974-2002 through insecticidal spraying and, from 1989, widespread distribution of ivermectin. The OCP is estimated by the WHO to have relieved 40m people from infection and prevented blindness in 600,000. A similar initiative (African Programme for Onchocerciasis Control or APOC) was started in 1995 to bring the disease under control in the remaining African countries, although it is thought that at least 15m people remain at risk. Equivalent programs are underway in LatAm.
WHO target	The WHO aims to have eliminated the disease in LatAm and Yemen by 2015 and in the remaining countries in Africa by 2020.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Soil-transmitted helminthiases (intestinal worms)

Figure 27: Soil-transmitted helminthiases overview

Cause	Infection with nematodes (several species eg, the roundworm *Ascaris lumbricoides,* whipworm *Trichuris trichiura* and hookworm *Necator americanus*), contracted by walking on faeces-contaminated soil.
Clinical manifestations	Worm infections, while rarely life-threatening, are generally associated with reduced nutritional status, increased absenteeism from school and work and decreased learning capacity.
Affected regions	A number of regions have endemic disease with India most affected (accounting for more than a quarter of at-risk children globally) followed by multiple countries in Africa, S.E Asia and LatAm. The WHO estimates that around 890m children globally need annual treatment with preventive anti-worming medication.
Treatment	The main treatment strategy is to provide regular anti-worming drug therapy, notably albendazole (donated by GSK) or mebendazole (donated by Johnson & Johnson). These are often given through school-based mass de-worming programs
Progress to date	Soil-transmitted helminthiases have been a focus of humanitarian efforts since the start of the 20th century when the Rockefeller Foundation promoted regular de-worming among children. The WHO has continued this work in endemic countries and by 2012 had achieved its target of 50% of affected countries having national plans of action for disease control. The WHO notes that elimination and eradication will not be achieved until the population areas involved have better access to sanitation, sewage treatment and disposal.
WHO target	The WHO aims for 75% of pre-school and school-aged children in need of treatment to be regularly treated by 2020 (50% by 2015). By 2020, the WHO expects 75% coverage of at-risk children to be achieved in all countries.

Source: WHO website, miscellaneous medical websites, Deutsche Bank

Food-borne trematodiases

Figure 28: Food-borne trematodiases overview

Cause	Infection with trematodes (aka flatworms or flukes) of various species. The four main disease types are clonorchiasis (caused by *Clonorchis sinensis*), opisthorchiasis (*Opisthorchis viverrini* or *O. felineus*), fascioliasis (*Fasciola hepatica* or *F. gigantica*) and paragonimiasis (*Paragonimus*). The natural hosts are, depending on trematode species, dogs, cats, sheep or cattle, and humans acquire infection principally by eating raw fish, vegetables or crustaceans which have become infested with larval stages.
Clinical manifestations	Infestation causes significant morbidity, with organ damage a particular risk, and the seriousness is often exacerbated by multiple rounds of infection which increase the number of worms in the body. Chronic infections with certain trematodes can be associated with a type of cancer of the bile ducts (cholangiocarcinoma) and can be life-threatening.
Affected regions	More than 70 countries are affected, mainly in Asia and LatAm. In 2005, a survey of just 17 countries found 56m affected individuals, of whom 8m had severe symptoms. Thus the true number of affected individuals is likely very large indeed. In addition to the human impact, annual livestock and fish production losses due to host infection are substantial.
Treatment	Treatment and prevention of foodborne trematodiases centres on medication with anti-helminth drugs. For regions at-risk of clonorchiasis and opisthorchiasis, praziquantel (donated by Merck KGaA) can be given annually. For fascioliasis, triclabendazole (donated by Novartis) can be used to treat infected individuals or annually as a preventative. For Paragonimiasis, each of the aforementioned drugs is a viable treatment option.
Progress to date	The WHO supports a public health strategy to combat disease and seeks for preventive medication to be a mainstream strategy by 2015. This has been aided by the efforts of some governments to conduct pilot studies of new strategies (eg, Bolivia and Peru established the effectiveness of triclabendazole treatment in fascioliasis in 2008).
WHO target	The WHO aims to have 75% of the at-risk population reached by preventive medicine by 2020.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Dengue – vaccine optimism

Background to dengue

Dengue is a mosquito-transmitted viral infection and is the second most widespread tropical disease after malaria. It is principally transmitted by the bite of female mosquitos of the species *Aedes aegypti* and cases are concentrated in S.E Asia, the Western Pacific, and Latin America. In most cases dengue presents as a flu-like illness with fever, joint pain and skin rash. However, it can develop into a life-threatening form, called severe dengue (or dengue haemorrhagic fever), which is characterized by internal bleeding and can be fatal. It is estimated the disease results in 25,000 deaths pa. Estimates vary as to the annual incidence (due to substantial under-reporting) but dengue is thought to affect between 50-390m people pa (of which 96m have clinically apparent disease and 2m are severely affected). As a consequence, the WHO classifies dengue as a major international health concern and includes it in its priority list of 17 neglected tropical diseases. The development of an effective dengue vaccine is a key pillar of the WHO's roadmap to reduce mortality and morbidity from the disease by 2020. Figure 29 provides a brief overview.

Figure 29: Dengue overview

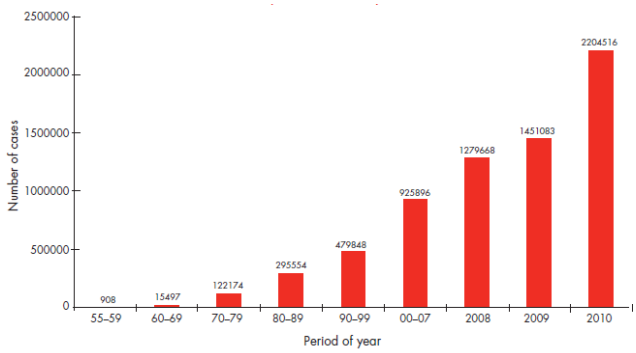
Cause	Dengue (also known as dengue fever) results from infection by a type of flavivirus (dengue virus). The disease is mainly transmitted by the bite of female mosquitos of the species *Aedes aegypti*, although transmission can also occur through blood transfusion and organ transplantation from infected donors. The dengue virus exists in four principal strains or serotypes (referred to as DENV-1, DENV-2, DENV-3 and DENV-4). Recent work in Thailand (announced in October 2013) suggests that a fifth serotype may also have arisen, although we note that the genetic variation in dengue viruses tends to be region-specific (ie, this putative new variant may not be present on a global basis).
Clinical manifestations	Initial infection results in an incubation period that is generally less than one week (maximum two weeks) before symptoms typically occur. For many the symptoms are mild (eg, slight fever) and the majority (80%) remain essentially symptom-free due to natural immunity. However, some patients develop a severe flu-like illness (with high fever, arthralgia, headache etc) and a measles-like skin rash. Furthermore a small proportion can develop a potentially fatal complication known as severe dengue (previously: dengue haemorrhagic fever) which involves internal bleeding and shock.
Affected regions	The WHO estimates that the incidence of dengue has increased by >30x in the last 50 years and the disease now represents a major global health threat. It is generally thought that the number of infections per annum has reached 50-100m in the >125 affected endemic countries (this compares with just 3 countries in 1955 and 8 in 1959). However, a recent publication in the journal *Nature* (Apr 25, 2013; 496(7446): 504–507) puts the number of annual infections far higher, at 390m. Given the expanded geographic reach, around half the global population is now theoretically at risk of infection, principally in LatAm, Africa, S.E Asia and the Western Pacific. Member states of the WHO reported around 4,200 deaths from dengue and over 2m cases of disease in 2010/11, both more than double the figure of five years earlier and both almost certainly massively under-reported (due to a combination of under-diagnosis in remote regions and misdiagnosis of dengue as other fever-bearing tropical diseases, notably malaria). Severe dengue is now a key cause of hospitalisation in Asia and LatAm.
Treatment	There are no specific medications for dengue and anti-viral approaches are still in an early research phase. Treatment therefore centres on supportive care (eg, rehydration, symptom alleviation and blood transfusion in more severe cases). The launch of an effective vaccine is a high priority, of which the most advanced is in development at Sanofi – this seeks to protect against the four main serotypes and has reported positive results from two pivotal Phase III trials. Mosquito control via insecticidal spraying, bednets and removing their natural breeding habitat (standing water sources) is a key component of disease control.
Progress to date	The WHO's *Global strategy for dengue prevention and control, 2010-2020* seeks to cut mortality and morbidity from the disease by 50% and >25% respectively and is based on a number of key elements. These include, amongst others, improved diagnosis and surveillance (including monitoring pandemic outbreaks), sustainable vector (ie, mosquito) control, and (once available) the implementation of vaccination. With no effective vaccine currently available (this is likely to change if, as we expect, the Sanofi vaccine becomes available in the 2015+ timeframe), current efforts focus more on prevention of transmission. The fact that *A. aegypti* was largely eradicated in the Americas by the early 1970s but has since resurged, with an accompanying rise in the number of dengue cases to a hyperendemic state, highlights the high importance of vector control.
WHO target	The WHO aims to have sustainable dengue vector control interventions established in 10 endemic priority countries by 2015. By 2020 it targets having dengue control and surveillance systems established in all regions and reductions in the number of dengue cases and deaths of >25% and 50% respectively (as compared with 2010).

Source: WHO website, Nature, miscellaneous medical websites, company data, Deutsche Bank

Unlike the majority of other tropical diseases, the incidence of dengue has risen substantially in the last 50 years and more recently it has spread from Asia and LatAm to the Southern USA, with cases also detected in Europe. In

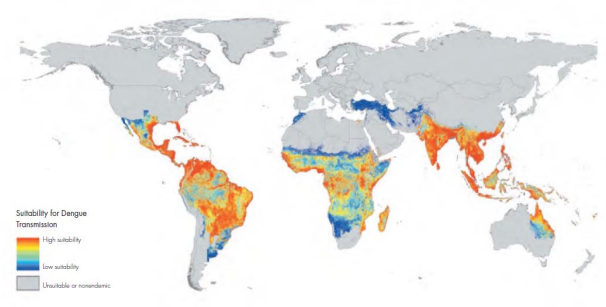
addition, dengue fever is now an important cause of morbidity in Western travelers and military personnel. With no vaccine or effective medication, treatment relies largely on oral or intravenous fluids, and preventative efforts have relied on mosquito control or avoidance. In addition to the burden on health, the disease has a significant economic impact on affected counties with aggregate costs in LatAm alone estimated at $2.1bn over 2000-7.

Figure 30: Reported severe dengue cases



Source: WHO Global Strategy for Dengue Prevention and Control

Figure 31: Dengue geographic distribution



Source: WHO Global Strategy for Dengue Prevention and Control

Multiple serotypes have complicated vaccine development

Dengue virus is a member of a group of viruses (flaviviruses) which also includes the yellow fever virus and Japanese encephalitis virus. Highly effective vaccines have been licensed for many years against these latter two diseases. However, dengue virus is actually a group of four closely related viruses (known as serotypes): DENV-1, DENV-2, DENV-3, and DENV-4 (note: researchers in Thailand recently claimed to have identified a fifth serotype but it is unclear whether this has been validated and/or is a purely regional variant). As a result vaccine developers have faced challenges in developing vaccines that will protect against all serotypes. Importantly, infection with any one of these four serotypes can produce clinical illness. In addition, there are often simultaneous or co-incident outbreaks with more than one serotype in any location. These co-incident outbreaks are often associated with more frequent cases of severe dengue fever or haemorrhagic fever. In addition, the serotypes affecting a particular region can vary from season to season. As such, it is important that vaccines protect against all four main serotypes.

Another complicating factor is that severe dengue is particularly associated with patients that have a low level of immune protection already (either passed from mother to baby or due to prior infection). This is theorized to occur due to 'antibody-dependent enhancement' in which preexisting, cross-reactive antibodies facilitate entry of the virus and cause worse outcomes. This also suggests that dengue vaccines must induce protective neutralizing antibodies to all four serotypes, to avoid enhancement of dengue after subsequent infection. For the widest possible adoption, a vaccine would ideally show a high level of protective efficacy (70%+ is usually deemed as optimal, albeit we understand the FDA would accept a lower bound for efficacy of >25%) against all four serotypes that lasts long enough to be meaningful (ie, at least 3–5 years). In addition, trials of vaccines must not only assess safety and immune response but also the long-term risks of exacerbating infection severity.

Sanofi's dengue vaccine candidate

Sanofi has been actively seeking to overcome the complexity of developing a dengue vaccine for more than two decades. In total it has invested over €1bn behind this program, mainly on R&D expenditure but also including €350m on a dedicated production plant in Lyon, France. After some earlier failures, the company now has a late-stage vaccine candidate (CYD TDV) which comprises four recombinant live attenuated vaccines (based on the yellow fever virus), each expressing antigens for one of the four dengue virus serotypes. The clinical development of this vaccine has been something of a rollercoaster:

- Early clinical studies in 6,000 children and adults were very encouraging, showing that the vaccine (given in three doses at months 0, 6 and 12) triggered the production of protective antibodies against all four serotypes with no reported safety concerns.
- In September 2012, Sanofi announced the results from a phase II proof-of-concept trial in c.4,000 Thai children. These showed that, despite a high level of immune response against all four serotypes, the vaccine only cut the incidence of dengue fever by 30% on a per-protocol basis (PP) and 35% on an intention-to-treat (ITT) basis, failing to meet statistical significance. Post hoc analysis showed that this failure was driven by inability of the vaccine to protect against one of the four serotypes (the incidence of DENV-2 fever was reduced by less than 10%). In assessing why the DENV-2 serotype evaded protection, it was suggested that this could be a peculiarity of the viral strain in Thailand which may differ from that prevalent in the rest of Asia and Latin America. Despite the disappointing efficacy findings, the vaccine was shown to be very safe with no cases of vaccine-related severe adverse events and no evidence that cases of dengue in vaccinated patients were any more severe than those in unvaccinated patients (ie, there was no indication of 'antibody-dependent enhancement').
- In April 2014, Sanofi reported positive headline results from the first of two pivotal Phase III trials of the vaccine, with efficacy (56.5%) close to double that seen in the Phase II proof of concept trial and the demonstration that the vaccine was associated with major public health benefits (in terms of reduced dengue-related hospitalizations and reduced severe dengue cases). Then in September 2014, headline data from a second pivotal trial were reported (efficacy: 61%), supporting the findings of the first pivotal trial. These two studies form the backbone of a Phase III development program (Figure 32) that includes over 31,000 individuals and will be used as the basis for regulatory filings. We discuss the Phase III results in more detail next.

Figure 32: Phase III trials of Sanofi's dengue vaccine, CYD TDV

Title	Aim	N=	Primary endpoint	Completion
Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia	To demonstrate that different CYD Dengue vaccine lots manufactured using the same method and in the same location but at different times produce an equivalent immunological response.	715	Immunogenicity of different lots of CYD dengue vaccine in terms of antibody levels against each of the four dengue virus serotype strains; 28 days post-dose 3 vaccination	Reported
Study of Yellow Fever Vaccine Administered With Tetravalent Dengue Vaccine in Healthy Toddlers	To evaluate whether the first CYD dengue vaccination can be administered concomitantly with Stamaril yellow fever vaccine during the same day and visit, but at 2 different sites of administration	792	Information on the antibody to yellow fever virus post Stamaril vaccination; 28 days post-vaccination	Jan' 13
Study of a Booster Injection of Pentaxim Vaccine Administered With Dengue Vaccine in Healthy Toddlers	To assess whether the second CYD dengue vaccination could be administered concomitantly with the booster vaccination of Pentaxim) during the same day and visit but in 2 different sites of administration	732	Information on the antibody to DTP, Filamentous haemagglutinin, polyribosylribitol phosphate (PRP) and polio post-Pentaxim booster vaccination; 28 days post-Pentaxim vaccination	Apr' 13
Study of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 Years in Asia	To assess the efficacy of the CYD dengue vaccine in preventing symptomatic, virologically-confirmed dengue cases	10,275	Virologically confirmed dengue cases occurring > 28 days after Dose 3	Headline data Apr'14
Study of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Latin America	To assess the efficacy of sanofi pasteur's CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases for dengue-endemic areas of Latin America	20,875	Virologically confirmed dengue cases occurring > 28 days after Dose 3	Headline data Sep'14
Study of a Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 11 Years in Malaysia	To evaluate the safety and immunogenicity of Phase III lots of the CYD dengue vaccine in a pediatric population in Malaysia	250	Safety of CYD dengue vaccine following each dose of vaccine up to 6 months post-dose 3	Jan' 13

Source: clinicaltrials.gov; Deutsche Bank

Phase III results are highly encouraging

The first of the two randomized Phase III studies tested three injections of the vaccine (or placebo) at six-month intervals in a total of 10,275 children (aged 2-14 years) from endemic areas of Indonesia, Malaysia, the Philippines, Thailand and Vietnam over 2011-13. Headline results showed a statistically-significant 56.5% reduction in dengue disease cases vs placebo – a substantially higher figure than the 30%/35% reduction seen in the smaller Phase II study (and comfortably ahead of the 25%+ efficacy boundary agreed with the FDA). At that time the only other specific figure released was the annual dengue incidence rate of 4.7% in the control group, which Sanofi noted demonstrates the high burden of disease in Asia. The company further noted that the initial safety data were consistent with the good profile seen in previous studies.

Additional key data from this trial was released four months later in the 11 July 2014 edition of 'The Lancet'. This showed that the vaccine had substantial benefits on public health, crucially helping to reduce cases of hospital admissions for dengue by two-thirds and cases of dengue haemorrhagic fever by close to 90% (Figure 33). Serious adverse events were not noted to be problematic (the incidence was 1% in each of the vaccine and control groups) and were stated by the study authors to be "*consistent with medical disorders in this age group and … mainly infections and injuries*." As for the earlier Phase II trial, the vaccine provided good protection against three of the four serotypes but serotype 2 (DENV-2) associated dengue cases were only reduced by 35% (this was not statistically significant on a PP basis but was significant on an ITT basis). While sceptics will highlight this as an issue, we would point out that the very substantial reductions in hospitalizations and severe cases were achieved even with this lesser efficacy against one serotype, indicating the overall strong proposition of the vaccine (see discussion below). Our view was echoed by the authors who concluded "*in view of the high disease burden in endemic countries, this vaccine candidate, despite moderate overall efficacy,*

could have a substantial effect on public health. That vaccination provided clinically important reductions in hospital admissions and prevented 80% of cases of dengue haemorrhagic fever is particularly noteworthy in this context."

Figure 33: Summary of results of dengue vaccine in Asian Phase III study

	Dengue incidence % (vaccine)	Dengue incidence % (control)	Vaccine efficacy %
Overall efficacy:			
Per protocol	1.8	4.1	56.5
ITT analysis	2.1	4.7	54.8
By serotype:			
Serotype 1	0.8	1.6	50.0
Serotype 2	0.6	0.9	35.0
Serotype 3	0.2	0.7	78.4
Serotype 4	0.3	1.0	75.3
Other measures:			
Efficacy vs dengue haemorrhagic fever			80.0*/88.5**
Efficacy vs hospitalised dengue			67.2

*Note: * after at least one injection; **after three injections; all other data presented for full three-dose course*
Source: The Lancet, 11 July 2014

Subsequently (on 3 September 2014), Sanofi reported headline results from the second pivotal Phase III efficacy study of the vaccine. This study was conducted in Latin America and included over 20,000 volunteers from Brazil, Colombia, Honduras, Mexico and Puerto Rico. The results were broadly similar to those from the first pivotal trial, with overall efficacy in fact slightly better (60.8% vs 56.5%) and safety in-line. Importantly - and in contrast to the first study - the vaccine was shown to demonstrate statistically-significant efficacy against all four circulating serotypes, including DENV-2 (Figure 34). Furthermore we note that the major public health benefits seen in the Asian study were replicated or bettered, with an even greater reduction in dengue-related hospitalisations (80.3% vs 67.2%) and a reduction in cases of dengue haemorrhagic fever that was stated to be "consistent" with that reported (88.5%) in the first trial. The full data will be reported in a peer-reviewed scientific journal and presented at the annual ASTMH (American Society of Tropical Medicine and Hygiene) meeting over 2-6 November 2014.

Figure 34: Efficacy of Asian and LatAm Phase III trials with dengue vaccine

%	Asian Phase III	LatAm Phase III
Overall efficacy	**56.5**	**60.8**
Type 1	50.0	50.3
Type 2	35.0	42.3
Type 3	78.4	74.0
Type 4	75.3	77.7
Reduction in dengue hospitalisations	67.2	80.3
Efficacy v severe dengue	88.5	"consistent"

Source: Company data, Deutsche Bank

We are particularly encouraged by the results for the second study, including the statistically-significant efficacy against all serotypes, as a number of epidemiology articles had suggested that DENV-2 is the most prevalent serotype in Brazil. For example, '*Clinical and Virological Descriptive Study in the 2011 Outbreak of Dengue in the Amazonas, Brazil*' (PLOS ONE; June 2014; Vol 9, issue 6) puts the incidence of DENV-2 at 46%, more than double that (21%) observed in the Asian Phase III study of Sanofi's dengue vaccine (Figure 35).

Figure 35: Incidence of dengue serotypes, Asia vs Brazil

Serotype	Asia (Phase III study)	Brazil (epidemiology study)
1	36%	10%
2	21%	46%
3	17%	9%
4	24%	29%
Co-infection/untyped	2%	6%

Source: The Lancet, www.plosone.org, Deutsche Bank

The debate over protection against three strains

While we view the overall dataset from Phase III as highly promising, there will inevitably be some debate about the lesser ability of the vaccine to protect against the DENV-2 serotype compared with serotypes 1, 3 and 4.

Detractors suggest that a lack of (or lower) protection against DENV-2 could be a meaningful disadvantage. In a March 2013 article in 'The Lancet' (*Dengue vaccine efficacy trial: does interference cause failure*?; Swaminathan *et al*), the authors cited concerns over the safety implications of providing protection against only 3 of 4 strains as a result of antibody-dependent enhancement. They noted that the results of dengue fever studies in Cuba had suggested a link between prior immunity to DENV-1 and the occurrence of severe disease in a DENV-2 led outbreak some two decades later. They suggested therefore that, given the risk of antibody-dependent enhancement, any reference to Sanofi's candidate vaccine as a "75% solution" would not be appropriate.

Our view is more positive, based on the cumulative clinical evidence to date and on the complex dynamics of the disease:

- First, as stated and emphasized in the July 2014 'Lancet' article, the vaccine was associated in the first Phase III study with very substantial reductions in hospitalizations (67%) and in severe dengue cases (80%+), which represent the most serious and costly facets of this disease for the public and payers. These important public health benefits were achieved *despite* the absence of meaningful protection against DENV-2. The second Phase III study, as noted, at least matched these public health benefits.
- Second, the authors of the 'Lancet' article noted that those who contracted dengue after vaccination had milder disease, with no evidence of enhanced disease over the 25-month observation period, ie, it remains the case that no clinical study yet has pointed to an antibody-dependent enhancement effect of the vaccine (hence resulting in worsening disease).
- Thirdly, we note that the worldwide prevalence and dynamics of dengue vaccine serotypes is complex and the geographic distribution changes over time (in Brazil, for example, DENV-4 was detected for the first time in the past decade and yet it was the second most prevalent type in the cited epidemiology study in 2011).
- Finally it is known that severe dengue outbreaks only seem to occur when multiple serotypes are circulating coincidentally. Thus a strategic campaign to reduce the transmission of three serotypes could still reduce the incidence and severity of dengue outbreaks.

Thus, we do not see the limited protection against DENV-2 as materially imperiling the prospects for approval and adoption of the vaccine.

First launches of the vaccine likely from late-2015

Assuming it gains the requisite regulatory approvals – which look highly likely to us, given the consistent positive Phase III results - Sanofi plans to launch the vaccine in late-2015 or early-2016 in at least one endemic country (likely a larger market such as Brazil, Mexico or Malaysia) and to roll it out thereafter as quickly as possible in remaining endemic countries. Crucially, with demand set to be very high (see below), the company began commercial production of the vaccine in July 2013 so that it will have sufficient inventory for launch (note: the Lyon plant is targeted to produce up to 100m doses pa from late 2017).

Sanofi has publicly stated that the market for such a vaccine could represent a €1bn+ commercial opportunity (assuming positive clinical data). Forecasting this opportunity, however, is complicated by a number of factors:

- Launches are likely to take place over several years across the key markets, beginning in the largest, most affected countries.
- Many of the >130 at-risk nations are amongst the world's poorest. As a result the company will have to adopt a tiered pricing strategy, with likely very low pricing (from less than $5 to $20/dose, ie, perhaps $15 to $60 for the full three-dose regimen) when dealing with supranational purchasing organisations (UNICEF, GAVI, PAHO).
- Estimates for demand based on predictive models[1] suggest that as many as 2.4-3.5bn doses could be theoretically required over the first five years of launch (with 75% delivered to the public sector). While capacity constraints would mean that Sanofi could not supply such vast quantities of vaccine, the huge demand nevertheless implies that, even with relatively low pricing, substantial sales are possible.
- Beyond the initial vaccination program, the annual birth cohort in the world's endemic regions (which numbers 45-50m pa) could generate a stable source of 'base' revenues.
- A further source of revenue could come from travelers to endemic regions. These individuals are likely to attract the highest pricing but immunization rates are likely to be very low (apart from perhaps the military) given that the vaccine requires three separate doses given over an extended period.
- Finally competition may arrive, albeit it is unlikely to be meaningful for at least several years. Inviragen (acquired by Takeda) is developing a dengue vaccine but this is not expected to enter Phase III until late-2014, and thus is unlikely to reach the market before 2020. Others looking at earlier-stage vaccines (which would likely be nearer 10 years from the market) include the US NIH, Merck, GSK and Novartis.

Taken together, in our base case we estimate that annual sales in the region of €1bn are achievable within 3-5 years of launch. This is based on the assumptions of: a medium-to-long term vaccination rate approaching 35% of the annual birth cohort (including much higher rates of c.70% in the most affected countries such as Brazil); 30% vaccination of the 'catch-up' cohort

[1] Forecasting dengue vaccine demand in disease endemic and non-endemic countries. Hum Vaccin. 2010 September; 6(9): 745–753. A. Amarasinghe et al.

over the first five years; and a modest (5%) vaccination rate in travelers. As 'catch-up' programs in the larger markets start to complete, we would expect sales to trend slowly downwards towards a 'base level' of €500-600m pa, reflecting the annual birth cohort and travel use. This would be much more in-line with current sales of the two leading selling vaccines in EMs, namely Pfizer's pneumococcal vaccine Prevnar (2013 sales: $876m/€660m) and GSK's competing vaccine Synflorix (2013 sales: £350m/$550m/€413m. Note that our model has previously assumed a 60% chance of success. Given the second Phase III trial success, we now de-risk our sales forecasts, adding 2% to our outer-year EPS and modestly lifting our target price (to €90/share from €87).

Figure 36: Preliminary sales model for Sanofi's dengue vaccine

	2015E	2016E	2017E	2018E	2019E	2020E	2021E
Annual birth cohort, m	48	49	49	50	50	51	51
Vaccination rate	*0%*	*5%*	*15%*	*24%*	*29%*	*33%*	*34%*
Infants vaccinated (m)	0	3	8	12	15	17	18
Doses (m)	0	8	23	36	44	50	53
Price (3 doses) $	30	30	30	30	30	30	30
Annual birth cohort sales	1	76	229	360	441	498	529
Catch-up cohort (aged 1-10), m	435	435	417	392	361	328	299
Vaccination rate	*0%*	*4%*	*6%*	*8%*	*9%*	*9%*	*7%*
Doses (m)	1	52	75	94	97	89	63
Price (3 doses) $	30	30	30	30	30	30	30
Catch-up sales	13	522	751	941	974	887	628
Travellers, m	5	5	5	5	5	5	5
Vaccination rate	*0%*	*1%*	*3%*	*4%*	*5%*	*5%*	*5%*
Doses (m)	0	0	0	1	1	1	1
Price (3 doses) $	150	150	150	150	150	150	150
Traveller sales	0	8	23	30	38	38	38
Total sales $m	15	605	1,003	1,331	1,453	1,422	1,194
In Euro m	**11**	**460**	**763**	**1,013**	**1,106**	**1,082**	**909**
Note: total doses (m)	*1*	60	98	131	*142*	*139*	*116*

Source: Deutsche Bank

Conclusion: Phase III results support prospects for widespread use (and blockbuster sales) of dengue vaccine

After more than 20 years of research and over €1bn in associated expenditure, Sanofi has achieved very encouraging Phase III results on its candidate dengue fever vaccine. The c.60% protection level and major public health benefits (reduced hospitalizations and severe cases) suggest there is a strong chance of widespread usage of the vaccine in the endemic regions. Resulting high levels of demand (modeled by some health statisticians in the billions of doses range in the first five years of launch) would likely generate sales approaching €1bn pa within 3-5 years, in our view, although sales would ultimately start to peak as 'catch-up' programs complete. Unlike many of the developments discussed in this report (eg, GSK's malaria vaccine) this product is not considered a philanthropic project by management (although pricing would be tiered for poorer countries) and it is set become a material EPS and revenue driver for Sanofi. The key risk is that the vaccine's weaker ability to protect against one of the four circulating serotypes of dengue (DENV-2) may limit reimbursement coverage in countries with a high relative incidence of this serotype. That said, the vaccine's *overall* efficacy is impressive and virus serotypes fluctuate with time, hence we do not see this as a major impediment to broad adoption.

Malaria – new drugs and vaccine on the way

Background to malaria

Malaria is a potentially life-threatening, mosquito-transmitted infection and is generally thought to be the most widespread tropical disease, affecting over 200m people pa (as noted, some recent estimates put dengue at a higher incidence) while 1.2bn globally are believed to be at high risk of infection. The infecting agent is a protozoal (single celled) parasite called *Plasmodium* which is transmitted by the bite of the female *Anopheles* mosquito. Most infected individuals experience fever, headache and vomiting but some will go on to develop much more serious disease, including organ failure, coma and death. Malaria remains endemic in tropical and sub-tropical countries, although concerted efforts to control the disease (reducing mosquito transmission via insecticidal spraying, bed nets and disrupting the mosquito's natural habitat of standing water) have seen major reductions in disease incidence (c.25%) and mortality (c.40%). Despite these strides, more than 600,000 people died from malaria in 2012, the vast majority (c.90%) in sub-Saharan Africa, illustrating the continuing scale of the problem. Of note, around three-quarters of deaths are in the under-five age group. Although drug resistance is a growing problem, malaria can be successfully treated with drug combinations based on artemisin or chloroquine (the preferred combination depending on the particular species of *Plasmodium,* with *P. falciparum* and *P. vivax* the most serious). International targets seek to reduce the incidence of the disease by 75% by 2015 but the limited improvements seen in sub-Saharan Africa are hampering progress towards this goal. Figure 29 provides a brief overview.

Figure 37: Malaria overview

Cause	Infection by a protozoan parasite called *Plasmodium*, which is transmitted via the bite of infected female *Anopheles* mosquitos. In the human body, the parasites reproduce in the liver, and then infect red blood cells. Several species of *Plasmodium* can infect and be transmitted by humans, the most serious (resulting in the majority of malaria deaths) being *P. falciparum* and *P. vivax* (by contrast *P. ovale*, and *P. malariae* are associated with a milder, generally non-life threatening type of malaria).
Clinical manifestations	Symptoms include fever, headache and vomiting, and typically appear 10-15 days after the initial mosquito bite. If not treated, malaria can disrupt the blood supply to vital organs, potentially resulting in coma and death.
Affected regions	97 tropical and subtropical countries have ongoing malaria transmission and an estimated 3.4bn people are at risk of disease, of whom 1.2bn are at high risk. In 2012, the WHO estimates that there were an estimated 207m cases of malaria and 627,000 deaths (of which 482,000 were children under the age of 5 years). Although cases present in the Americas and Asia, the overwhelming majority (c.90%) of malaria deaths occur in sub-Saharan Africa, with c.40% arising in just two countries: Nigeria and the Democratic Republic of the Congo.
Treatment	Artemisin-based combination therapies (ACTs) are recommended as the first-line treatment for malaria caused by *P.falciparum*, although resistance has been observed in four SE Asian countries (Cambodia, Myanmar, Thailand, Vietnam). Novartis is the main supplier to the WHO, based around its ACT, Coartem (the first to be introduced and the first available in a paediatric form) In such combinations the artemisin derivative, artesunate, is given along with a second anti-malarial drug such as mefloquine. The WHO recommends chloroquine for the treatment of *P. vivax* malaria where the drug remains effective (resistance has been seen in 10 countries so far) or, if resistance is encountered, ACTs. Alongside treatment, insecticidal spraying and insecticidal bed nets are recommended although only a small proportion of those in endemic regions benefit from these. (eg, 200m nets are expected to be distributed in 2014, after 136m in 2013). Insecticidal treatment and disruption of the mosquito's habitat (ie, standing water) also forms part of a multi-pronged disease control strategy. While no vaccine is yet available, GSK hopes to receive WHO coverage for its recombinant vaccine Mosquirix in 2015 (although the protection rate of c.30% is not optimal).
Progress to date	The WHO reports that between 2000-2012, intensified efforts at disease treatment and control helped to reduce malaria incidence rates by 25% globally (31% in Africa) and the global mortality rate by 42% (49% in Africa). This amounted to saving an estimated 3.3m lives, of which 90% were in the under-5 age group in sub-Saharan Africa.
Global targets	The World Health Assembly and Roll Back Malaria target a reduction in the incidence of malaria cases of 75% by 2015. Only a minority of the population at risk globally has benefited from this due to the need for more decisive action in sub-Saharan Africa. The Millennium Development Goal also targets reversing the incidence of malaria over 2000-15.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Current drug treatment; Novartis a key supplier

Artemisin-based combination therapies (ACTs) are recommended as the first-line treatment for malaria caused by *P.falciparum*, although resistance has been observed in four SE Asian countries (Cambodia, Myanmar, Thailand, Vietnam). ACTs generally comprise the artemisin derivative, artesunate, along with a second anti-malarial drug such as mefloquine. For the treatment of *P. vivax* malaria, the WHO recommends chloroquine or alternatively, if resistance is encountered (as seen in 10 countries so far), ACTs. The use of artemisin monotherapy is strongly discouraged by the WHO in order to prevent the development of resistance to this key anti-malarial component.

For those living in areas of moderate-to-high malaria transmission in sub-Saharan Africa, the WHO additionally recommends preventative medication regimes. These include: intermittent preventative treatment in pregnancy (IPTp) with a combination of sulfadoxine and pyrimethamine (SP); intermittent preventative treatment in infants (IPTi) with SP, given alongside paediatric vaccination schedules; and seasonal malaria chemoprevention (SMC) in the 3-5 age group with a combination of amodiaquine and SP (AM+SP).

A number of pharmaceutical manufacturers supply the WHO/UNICEF and the Affordable Medicines Facility-malaria initiative (AMFm; part of the Global Fund to fight AIDS, Tuberculosis and Malaria) with quality-assured, low price ACTs and the WHO reports that (based on data from eight manufacturers) the number of delivered treatment courses burgeoned from 11m in 2005 to 331m in 2012. This was helped by a substantial increase in international funding over the past decade (from <$100m in 2000 to $2bn in 2012, with domestic financing adding a c.$0.5bn). However, it is estimated that approximately $5bn pa of funding is required to provide universal access to malaria treatment and prevention. Indeed access is the real problem here: estimates suggest that up to half of malaria patients in Africa do not have adequate access to public health services (notably in urban townships and remote rural villages) and that less than 20% of children with malaria and fever actually receive an ACT.

The largest supplier of ACTs is Novartis. Through an initial 10-year partnership with the WHO the company has provided more than 600m treatment courses free of charge since 2001 (this partnership was renewed under the same terms in 2011). Importantly, Novartis was the first company (in 1999) to supply a fixed-dose combination of artemisin and lumefantrine, known as Coartem. This became the first ACT to be included in the WHO's Model List of Essential Medicines (in 2002) and the combination accounts for more than three-quarters (77%) of all ACTs delivered. Building on this, Novartis was able to develop and launch the first paediatric ACT, a fast-dissolving, palatable (sweet-tasting) tablet version of Coartem (known as Coartem Dispersible) in 2009. It has since supplied over 200m tablets of this child-friendly anti-malarial combination to 40 countries, mostly in Africa. As an example of its continuing efforts to help control the disease, in April 2014 Novartis announced the delivery of 2m Coartem Dispersible tablets to Zambia in conjunction with Malaria No More's 'Power of One' campaign. This new campaign is sponsored by Novartis and matches public donations with donations from the company (in this case 1m apiece). Novartis coordinates its activities in this disease area, including the provision of on–the-ground-infrastructure, medical training etc, through the Novartis Malaria Initiative (Figure 38), which it believes to be one of the largest access-to-medicine programs in the healthcare industry.

Figure 38: Key elements of Novartis Malaria Initiative

Initiatives
Non-profit partnership with WHO established in 2001 (renewed in 2011) that has supplied >600m treatments to public sector in Africa, including first paediatric combination Coartem Dispersible
Delivered >90m treatments to private sector in Africa through Affordable Medicines Facility - malaria (AMFm) since 2010
Access program for private sector established in 2012 to improve distribution channels, train field staff on ACT use and patient education, distribute treatments (with emphasis on infants/children), monitor availability and retail prices of ACTs
Sponsorship of the Malaria No More's 'Power of One' campaign whereby Novartis will match public donations of ACTs
Participation in SMS for Life project, which uses mobile phone technology to track weekly stocks of ACTs to prevent stock-outs in the supply chain
Running workshops since 2006 with managers of National Malaria Control Programs (NMCP) in Africa to share best practice in diagnosis, treatment and technical assistance
Training health workers in clinical trial conduct (pharmacovigilance, safety monitoring etc) to encourage and facilitate clinical testing of candidate drugs and vaccines to international GCP standards
Training health workers in the diagnosis and treatment of malaria and provision of public health education initiatives such as workbooks, disease awareness booklets/posters etc
Supporting farmers and suppliers in China and Madagascar in production of artemisia annua, the plant source of key anti-malarial drug artemisin

Source: Novartis website, Deutsche Bank

Future treatment options (GSK, Novartis, Sanofi)

The international pharmaceutical manufacturers' body, IFPMA, and the WHO established the Medicines for Malaria Venture (MMV) in 1999. This not-for-profit public-private partnership seeks to fund and manage R&D into new treatment and prevention options for malaria, supported by a network of public, private and philanthropic organizations. Three of the eight participating pharmaceutical companies are represented by the European large-caps, namely GlaxoSmithKline, Novartis and Sanofi (the others are Merck & Co., Pfizer, sigma-tau spA, Chong Qing Holley and Shin Poong). Novartis' paediatric Coartem formulation discussed earlier was introduced in conjunction with the MMV. Figure 39 highlights the current development portfolio of medicines.

Figure 39: Global portfolio of anti-malarial medicines (EU large caps shaded)

Product/phase	Manufacturer
Registration	
Mefloquine Artesunate	Farmagiulinhos/DNDI
Artesunate i.r.	WHO/TDR
Arterolane/PQP	Ranbaxy
Naphthoquine/artelmisin	ARCO
Phase IIb/III	
Tafenoquine	GSK
Pyramax Paediatric	Shin Poong/University of Iowa
Eurartesim paediatric	Sigma-tau
ArtiMist	Proto Pharma
Phase IIa	
KAE609	Novartis
KAF156	Novartis
Ferroquine	Sanofi
SAR97276	Sanofi
OZ439	Monash/UNMC/STI
Artemisone	UHKST
Fosmidomycin piperaquine	Jomaa Pharma GmbH
Methylene Blue AQ	Uni. Heidelburg

Source: Medicines for Malaria Venture website (Phase IV projects not included)

As can be seen, many of the products in development are ACT variations or paediatric formulations based on existing drugs. However, within this list we highlight the following novel developments:

- Novartis is working on two new classes of next-generation anti-malarials for *P. falciparum* malaria (and potentially *P. Vivax*). The most advanced compound, KAE609 (cipargamin), is in Phase II. It is a novel synthetic spiroindolone molecule and was awarded MMV Project of the Year 2009. A 10-patient single-dose efficacy and safety study is due to complete in February 2015. The *New England Journal of Medicine* (31 July 2014) reported the results of an open-label Phase II study which showed that 30mg of KAE609, taken once-daily for three days, cleared parasites very quickly (median time: 12 hours) in 11 patients with *P. falciparum* infection and 10 with *P. vivax* infection. This was the first time an antimalarial drug with a novel mechanism of action had achieved clinical proof of concept in over 20 years. The second compound, KAF156, also belongs to a novel class (the imidazolopiperazonines or IZPs) and targets the parasite at both blood and liver stages of the disease (and thus could have broader efficacy). It is hoped that each compound may represent a one-dose cure. Behind these two compounds, Novartis has identified a third target (P14K) for preventing and treating malaria. As noted, Novartis already has a major involvement in malaria treatment and support (through the Novartis Malaria Initiative). Its research work is conducted via the Singapore-based Novartis Institute for Tropical Diseases (NITD) in conjunction with MMV. The NITD includes more than 100 scientists and support staff and focuses on dengue, TB and malaria. Any resulting treatments will be made available on a not-for-profit basis to poor patients in countries where these diseases are endemic
- GlaxoSmithKline is developing tafenoquine for the treatment and relapse prevention of *P. vivax* malaria (the form of malaria that is prevalent in SE Asia and LatAm). Together with MMV it announced the start of a Phase III program in April 2014 which will include two randomized, double-blind trials in adults infected with *P. vivax*. The first ('DETECTIVE') will investigate use of the drug in combination with chloroquine as a radical cure (preventing relapse in patients with dormant infection, a feature of this type of malaria). The second trial ('GATHER') will be a head-to-head study versus primaquine, the only approved drug for radical cure. The details for DETECTIVE are not yet published but clinicaltrials.gov states that GATHER will include 300 patients and estimates trial completion in November 2015. GlaxoSmithKline's research in malaria is conducted from its dedicated DDW (diseases of the developing world) R&D facility in Tres Cantos, Spain. There are over 100 scientists at Tres Cantos (focusing on malaria, TB and NTDs, such as leishmaniasis, sleeping sickness and Chagas), of which 30 are supported by MMV, and it targets diseases of high socio-economic need rather than commercial return.
- Sanofi entered into a collaborative agreement with MMV in 2008 covering a number of putative anti-malarial compounds, of which ferroquine remains in its portfolio. Currently in Phase II, this 4-aminoquinoline compound is designed for use against drug-resistant *P. falciparum*, having shown activity in vivo and in vitro against chloroquine-resistant strains. Originally looked at as a monotherapy, Sanofi is investigating its use in combination with a second novel anti-

malarial the synthetic ozonide OZ439 (which has a similar mechanism of action to artemisin, releasing destructive free radicals from a peroxide chemical 'bridge'). OZ439 was originally donated to MMV by Roche in 2003. While no studies are currently listed on clinicaltrials.gov, the MMV website notes that "*drug-to-drug interaction safety studies with OZ439 and ferroquine as well as efficacy studies in human volunteers support the further development of this combination. The team is now preparing a Phase IIb study*."

Vaccine potentially coming from GSK in 2015

Beyond novel anti-malarial drugs and combinations, prevention with a vaccine would clearly represent a major (and cost-effective) advance in controlling malaria, especially given the growing resistance to current drug regimens. A number of vaccine approaches have been tested over the past several decades without success so far. Particular challenges have been presented by the *Plasmodium* organism's advanced structure (as compared with viruses and bacteria) which changes during the course of its complex life cycle: the parasite initially enters the liver ('pre-erythrocytic' or 'hepatic' phase) before invading red blood cells ('erythrocytic' or blood phase) and at each stage its surface antigens change. The ideal vaccine would elicit antibodies to prevent the parasites from reaching the liver and also produce a strong white cellular (T-cell) response to block or kill infected liver cells.

The most clinically advanced candidate vaccine for *P. falciparum* malaria is RTS,S (which looks set to be branded as 'Mosquirix'). This is being developed by GSK and will soon come to the end of a large-scale Phase III trial in more than 15,000 infants and young children in Africa. The vaccine is administered as three doses (one month apart) and contains a surface antigen (circumsporozoite protein or CSP) which is present in the parasite's pre-erythrocytic stage, together with an antigen from the Hepatitis B virus and the adjuvant AS01 (the additional antigen and adjuvant were included to elicit a stronger immune response after earlier work showed the CSP antigen alone was insufficiently immunogenic). GSK has been developing this vaccine since the late 1980s, initially testing it in US volunteers and, since 2001, in children in sub-Saharan Africa in collaboration with the non-profit PATH Malaria Vaccine Initiative (MVI). To date GSK has invested over $350m in developing the vaccine and over $200m of additional financial support has been provided by the Bill & Melinda Gates Foundation.

Good (>60%) levels of protection were seen with RTS,S in a pilot Phase II trial. Unfortunately the results to date from the huge Phase III trial have not replicated the Phase II findings. Final data (showing protection at 32 months and examining the impact of a fourth 'booster' injection given 18 months after the usual three-dose course) are due to be reported later this year. However, GSK has already reported protection levels at 12 and 18 months in the two age groups under study, toddlers (5-17 months) and babies (6-12 weeks). In the former, protection was 56% at 12 months, falling to 46% at 18 months. In babies, however, the levels of protection were appreciably lower, at 31% and 27% respectively, ie, roughly half that seen in Phase II. The latter is disappointing as the vaccine would ideally be included as part of the routine vaccination schedule for babies (vaccination of toddlers is of course possible but would require additional resources and medical infrastructure). Bill Gates noted "*the efficacy came back lower than we had hoped, but developing a*

vaccine against a parasite is a very hard thing to do. The trial is continuing and we look forward to getting more data to help determine whether and how to deploy this vaccine."

Figure 40: Efficacy from the Phase III trial of Mosquirix (RTS,S)

Protection	5-17 months age group	6-12 weeks age group
- from clinical malaria at 12 months	56%	31%
- from severe malaria at 12 months	47%	37%
- from clinical malaria at 18 months	46%	27%
- from severe malaria at 18 months	36%	15%
- from hospitalisations at 18 months	42%	17%

Source: company data, Deutsche Bank

The New England Journal of Medicine published the results in 5-17 month old children at the end of 2011 (NEJM;365:1863-75) and in 6-12 week old babies at end-2012 (NEJM 367;24;2284-95) and the authors offered a number of possible explanations for the lower protection in babies. These included the possibility of interference from residual maternal immunity or from other co-administered paediatric vaccines (pentavalent DTP/Hib/HepB and oral polio) and the absence of prior priming with the HepB component of the pentavalent vaccine (which may have helped the response in toddlers). Either way, the final data at 32 months and with a booster dose will be key to determining the enthusiasm for approving this vaccine and incorporating it into the WHO's malaria program. Thus GSK noted in its October 2013 press release on the 18-month data that it "*intends to submit, in 2014, a regulatory application to the European Medicines Agency (EMA). The World Health Organisation (WHO) has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015 if it is granted a positive scientific opinion by the EMA.*" The filing took place in July 2014 so that a policy decision by the WHO is possible by end 2015. This would allow large-scale usage of the vaccine by malaria-endemic African countries through national immunization programs.

We assume the final Phase III data – though likely to be sub-optimal given the results so far - will nevertheless be sufficiently positive when set against the unmet need to gain the requisite scientific opinion from the EMA during 1H15 (using the Article 58 procedure, whereby it assesses the efficacy, safety and quality of a medical product in collaboration with WHO). From 2016 onwards, we calculate the RTS,S vaccine could generate recurring sales in the broad range of $30-50m pa. This is based on the annual birth cohort in sub-Saharan Africa of c.32m pa, a 30-50% uptake rate and a price per three-dose course of approximately $3 (note: prices paid by UNICEF for vaccines range from well under $1/dose for older paediatric vaccines to roughly $5/dose for more recently-launched HPV and rotavirus vaccines and $7 for pneumococcal vaccine). Importantly, GSK has committed to setting pricing at a level which covers the manufacturing cost plus a 5% return which it will reinvest in R&D on malaria and other tropical diseases. Thus this is a non-profit initiative by GSK and its involvement is philanthropic, matching the aims of its partners. This is in contrast to the dengue fever vaccine under development by Sanofi, discussed earlier in this report.

Initial use of the vaccine would likely generate sales in excess of the figures cited above, in our view, due to catch-up vaccination of a proportion of the under-5 age group in whom the protection levels look more compelling (c.50% to date as discussed). If, for example, an additional 30-50% of the under-5s were vaccinated over the first three years of launch, this would – using the

same pricing assumptions – generate 'catch-up' sales averaging $50-80m pa over 2016-18, taking total annual sales of RTS,S/Mosquirix to perhaps $80-130m. This would be material in the context of GSK's overall EMs vaccines business (2013 sales: £1,124m/$1,765m) but clearly not on a group-wide basis (2013 group sales: £26.5bn/$41.6bn). As stated these revenues would generate no profit for GSK, reflecting the philanthropic nature of the project.

Conclusion: progress but access, resistance the key issues

Malaria is a treatable disease but the WHO and Roll Back Malaria target to cut the incidence of disease by 75% is notably being hindered by access issues in sub-Saharan Africa. A substantial uplift in international funding between 2000-2012 has seen delivered anti-malarial treatment courses burgeon to over 300m pa (from just 11m in 2005), led by Novartis, the originator of ACT and the first to develop a child-friendly combination. However, up to half of malaria patients in Africa lack sufficient access to health services to benefit from treatment. Capacity building programs (improved medical training, securing the supply chain etc) such as those incorporated within Novartis' Malaria Initiative are thus vital to help get treatment in a timely manner to the affected and at-risk population. Growing resistance to treatment poses an additional challenge but several novel drugs are in development (notably from Novartis, GSK and Sanofi) that may offer effective, alternative treatment approaches. Developed in conjunction with MMV and other partners these putative new drugs represent philanthropic (rather than commercially targeted) efforts by the companies concerned. Finally, 2015 could see the WHO adopt coverage of the first ever malaria vaccine (Mosquirix; RTS,S), supplied on a not-for-profit basis by GSK. While the efficacy of this vaccine in infants in particular looks likely to fall short of initial hopes (c.30% protection rate in Phase III data reported so far), low pricing and the high disease burden suggest it could be widely adopted in key countries in sub-Saharan Africa (eg, Nigeria, Democratic Republic of Congo).

Other diseases affecting the tropics – Ebola, HIV and TB

Ebola virus

First noted in 1976, infection by the Ebola virus (spread by fruit bat bites and subsequent human-to-human transmission) has resulted in a series of sporadic but deadly outbreaks in several Central and West African countries. An outbreak this year, however, is much the most devastating ever recorded, resulting to date in >2,100 reported deaths and >4,000 cases across Guinea, Sierra Leone, Liberia and Nigeria (with the WHO suggesting that as many as 20,000 people may ultimately contract the disease by the time it is under control). To put the 2014 outbreak into context, the highest number of fatalities previously recorded were in 1976 (431 deaths), 1995 (254), 2000 (224) and 2007 (224), while no Ebola deaths were recorded in 22 of the past 38 years. No specific treatment is available and the disease, which is referred to as Ebola virus disease or Ebola hemorrhagic fever, is usually (in 50-90% of cases) fatal.

Concerted international efforts are underway to develop a treatment or vaccine. In the mean time, the WHO has determined that the current outbreak is an "extraordinary event" and that it is ethical to offer unregistered drugs and vaccines, despite unproven clinical profiles. A combination of monoclonal antibodies (ZMapp) under development by Mapp BioPharmaceutical gained considerable coverage when it was used to treat two US citizens and a Spanish priest and the remaining limited drug supply was sent to Liberia (the hardest-hit country). Elsewhere Tekmira Pharmaceuticals is developing an antisense (RNAi) treatment for the Zaire species of Ebola (ZEBOV) which entered Phase I in January 2014. Sarepta Therapeutics also lists an antisense compound for Ebola (AVI-7537) in Phase I. Several companies (GSK, NewLink Genetics, Inovio, Vaxart, J&J) along with the US National Institutes of Health and the Canadian government are working on experimental vaccines and are attempting to expedite development. Most advanced is GSK which this month began a safety trial in volunteers, using a candidate vaccine comprising a vector primate virus and a protein from the ZEBOV strain of Ebola (which has shown promising protection data to 10 months in four macacque monkeys in a paper in Nature). GSK hopes to complete this study in just 3 months.

Figure 41: Ebola overview

Cause	Infection by the Ebola virus, which is transmitted via the bite of fruit bats (the natural host organism) or to a lesser degree by the bite of animals which have been infected by bat bites (eg, monkeys, porcupines). Outbreaks are then amplified by direct human-to-human contact (via body fluids). The 2014 outbreak has been largely the result of human-to-human transmission. Five distinct forms of the virus have been observed (BDBV, ZEBOV, RESTV, SUDV, TAFV), their names reflecting their geographic occurrence (eg, SUDV = Sudan Ebolavirus). Of these, RESTV (which can be seen in Asia) has not been known to cause morbidity or mortality. However, the fatality rate is up to 90% during outbreaks with other forms of the virus.
Clinical manifestations	Symptoms include fever, headache, vomiting, diarrhea, internal and external bleeding and typically appear 2-21 days after the infecting bite. The disease is usually fatal, especially if untreated. The fatality rate in the 2014 outbreak has been around 50% but in previous outbreaks it has been as high as c.90%
Affected regions	Principally Central and West Africa, especially near rainforests and in distant villages with limited healthcare access.
Treatment	Intensive care (fluids, symptom control) is the only available treatment as no licensed drug or vaccine exists. Containment of the disease (through quarantining and slaughter of animal pools) and health education are key elements in controlling outbreaks, which typically occur in any given region for approximately 2-4 months. The 2014 outbreak has been exceptional both in its scale and in its longevity (the first cases were reported in Guinea in March 2014, six months ago).

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

HIV/AIDS

Although HIV/AIDS is not specifically a tropical disease, it is highly prevalent in the tropics. In particular, the WHO estimates that over two-thirds (68%) of the 35m people infected with the virus are living in sub-Saharan Africa (Figure 42) and that around 1:20 adults are infected in the region. The WHO co-sponsors the Joint United Nations Programme on AIDS (UNAIDS) and its '*Global health sector strategy for HIV/AIDS for 2011-15'* supports the use of a coordinated package of diagnostic, treatment, prevention, education and support measures to combat the disease. Compared with a 2009 baseline, its 2015 targets are to reduce new HIV infections in young people (15-24 years) by 50%, to cut new infections in children by 90% and to reduce HIV-related deaths by 25%. It also seeks to cut tuberculosis (TB) related deaths by 50% versus a 2004 baseline as TB is a frequent co-infection in patients with HIV (affecting around a third).

Figure 42: Regional HIV and AIDS statistics (2012)

Region	Incidence of HIV infection	New HIV infections	Adult HIV/AIDS prevalence	AIDS deaths
Sub-Saharan Africa	25.0m	1.6m	4.7%	1.2m
S/SE and E Asia	4.8m	0.4m	0.3%	0.3m
Latin America	1.5m	0.1m	0.4%	<0.1m
E Europe & C. Asia	1.3m	0.1m	0.7%	0.1m
North America	1.3m	<0.1m	0.5%	<.01m
Western/Central Europe	0.9m	<0.1m	0.2%	<.01m
Other	0.6m	<0.1m	0.2%	<.01m
Total	35.3m	2.3m	0.8%	1.6m

Source: WHO website, Deutsche Bank

Anti-retroviral therapy (ART) can in many cases provide highly effective long-term treatment for HIV-infected individuals. It can also be utilised as a preventative approach in those with HIV-positive partners and for blocking maternal transmission of HIV to the unborn child. Under the WHO's coordinated global strategy, the use of ART has grown very significantly (eg, by 20% in 2012 alone), in part facilitated by drug manufacturers (eg, Gilead and GlaxoSmithKline's ViiV joint venture) offering their ARTs at much-reduced prices to developing countries and sharing their intellectual property with local generic manufacturers via the Medicines Patent Pool (MPP). However, considerable work still needs to be done in improving access given that the WHO estimates that only a third (9.7m) of the c.26m patients eligible for ART in low- and middle-income countries actually received treatment in 2012.

Figure 43: HIV/AIDS overview

Cause	Infection by the retrovirus human immunodeficiency virus (HIV). The virus spreads through transfer of human bodily fluids (mainly as a result of unprotected sex, unscreened blood transfusions, shared syringes/needles, and ingesting breast milk).
Clinical manifestations	As the virus uses key human immune cells (CD4, macrophages) as the host for its replication, infection leads to progressive loss of immune function and an increased incidence in opportunistic infections and cancers. Initial clinical symptoms include a brief flu-like illness (which signals seroconversion), typically within 2-6 weks of viral transmission, following which the infection is often asymptomatic or 'silent' for several years. The spread of virus, if unchecked, will ultimately (often after 10-15 years) damage the immune system sufficiently such that the individual becomes susceptible to serious infections such as pneumonia, TB and certain cancers (eg, the characteristic skin cancer, Kaposi's sarcoma). Late-stage disease is referred to as AIDS.
Affected regions	The disease is present globally and affects an estimated 35.3m people. However, the WHO estimates that 25m (68%) of those infected with the virus are living in sub-Saharan Africa (with around 1:20 adults infected). Countries with a high incidence include South Africa, Zimbabwe and Mozambique. S/SE Asia (4.8m) and LatAm (1.5m) are the next highest in incidence
Treatment	The WHO recommends a standard treatment approach which combines a minimum of three antiretroviral drugs (antiretroviral therapy or ART) to suppress the virus and prevent further disease progression. Preventative use of ART is also recommended for HIV-positive pregnant women and in certain populations deemed to be at high risk of infection. Key drug components of ART regimens include Epivir/3TC and Retrovir/AZT (both developed by GSK), Truvada/emtricitabine + tenofovir (Gilead), Sustiva/efavirenz (Merck & Co.), and Viramune/nevitapine (Boehringer Ingelheim). The newest drug in the armamentarium is the integrase inhibitor Tivicay/dolutegravir (from GSK's ViiV j/v). These drugs are typically made available at very low cost by the manufacturers concerned and locally manufactured generics are common in endemic regions due to voluntary sharing of IP rights via the Medicines Patent Pool. In addition to the use of ART, the WHO's *'Global health sector strategy for HIV/AIDS for 2011-15'* supports the use of a coordinated package of diagnostic, educational and support measures to combat the disease.
Progress to date	The WHO updated its guidelines for eligibility for ART in 2013, which more than doubled the number of potential recipients to over 28m. It specifically targets 15m people globally receiving ART in 2015 (vs 9.7m at end 2012) and estimates that over 4m lives have been saved by ART provision so far. In addition, in 2012, over 60% of pregnant HIV-infected women received ART to block maternal transmission of the virus to the unborn child or infant.
Global targets	The WHO targets reductions in new HIV infections in young people (15-24 years) of 50%, in children of 90% and in HIV-related deaths of 25%, all compared with a 2009 baseline. It also seeks to cut TB related deaths by 50% vs a 2004 baseline. Its updated 2013 guidelines target a 36% reduction in annual HIV infections by 2025 and a 39% reduction in related deaths.

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

TB (tuberculosis)

TB is not a tropical disease *per se* but, like HIV/AIDS, is strongly present in the tropical regions of the world (eg, SE Asia, sub-Saharan Africa). As noted above, it is also a frequent co-infection with HIV (affecting one third of patients). The disease is spread by human contact (mainly through aerial transmission by coughing, sneezing etc). Despite the availability of curative treatment with a four-drug regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), the WHO estimates that TB is the second leading cause of death globally (after HIV/AIDS) from a single infectious agent, with 8.6m contracting the disease in 2012 and 1.3m dying from it.

Effective treatment and containment of the disease is threatened by poor compliance (recommended regimens require 6-30 months treatment time) and by the growing incidence of multi-drug resistant TB (MDR-TB). Expanding on the latter point, around 0.5m people (of the 8.6m referenced above) were estimated to have been infected with resistant bacteria in 2012. The WHO recommends the oxazolidinone anti-bacterial Linezolid (manufactured by Pfizer) in cases of drug-resistant TB although its efficacy is stated to be "unclear". The bulk of industry R&D efforts now target resistant disease, eg, in 2013, the FDA approved J&J's Sirturo (bedaquiline), a quinolone derivative for MDR-TB while AstraZeneca is progressing AZD5847, an oxazolidinone anti-bacterial (the same class as Linezolid), in Phase II studies. Recently (in August 2014), Novartis announced a licensing agreement under which it will transfer its TB R&D program to the Global Alliance for TB Drug Development ('TB Alliance'): the portfolio includes a novel pre-clinical indolcarboxamide compound NITD304 with activity against drug-sensitive and MDR-TB.

Figure 44: TB overview

Cause	Infection by the bacterium *Mycobacterium tuberculosis*. This infects the lungs primarily and is spread by direct human transmission (through inhalation of bacteria in the vicinity of an infected individual coughing, sneezing or spitting).
Clinical manifestations	Symptoms include fever, cough, sweating at night and weight loss and can be very mild for months (a latent form also exists which can be symptom-free and non-infectious for prolonged periods). Without treatment, however, up to two thirds of cases can be fatal and those with compromised immune systems (eg, co-infection with HIV/AIDS) are at particular risk.
Affected regions	The disease is present globally but more than half of new cases are observed in Asia and the highest incidence (new cases/population) is seen in sub-Saharan Africa
Treatment	A curative four-drug regimen of isoniazid/rifamicin/pyrazinamide/ethambutol for two months followed by isoniazid/rifampicin for four months is recommended for those with active disease. Less than 10% of cases which adhere to this regimen then relapse (compliance is a particular problem). Latent disease involves 6-9 months treatment with isoniazid monotherapy. The WHO also promotes its Stop TB strategy which includes financing, health education, diagnosis, and assured drug supply.
Progress to date	The WHO reports that the number of infections globally is falling slowly and that the death rate from TB dropped by 45% between 1990 and 2012.
Global targets	The Millennium Development Goal seeks to reverse the spread of TB by 2015 while the WHO seeks to cut TB related deaths in 2015 by 50% vs a 2004 baseline. Longer term, the WHO seeks to reduce the incidence of TB and the number of TB deaths by 50% and 75% respectively between 2015-2025 (with reductions of 90% and 95% to be achieved by 2035).

Source: WHO website, miscellaneous medical websites, company data, Deutsche Bank

Company profiles

Introduction

We surveyed each of our European large-cap coverage companies on their exposure to - and ambitions in - tropical diseases and have used the results, together with other sources (eg, company corporate social responsibility reports, the detailed Access to Medicine Index company sections and relevant WHO and NTD websites and publications), to produce the following profiles.

Note that we do not here include profiles for AstraZeneca and Novo Nordisk as neither has a meaningful current exposure to tropical diseases:

- As noted earlier, however, Novo ranks strongly (#6) in the Access to Medicine Index 2012 due to its global leadership role in insulin supply and the extensive access programs that it works around this.
- Furthermore, AstraZeneca has multiple access programs and activities in the developing world in its core therapy areas (eg, respiratory) as well as an active R&D program in TB (with a drug, AZD5847, undergoing Phase II trials). It was also a founding supporter of WIPO Re:Search, the public database of IP and resources for R&D for NTDs, tuberculosis, and malaria. Its slippage in the Access to Medicine Index to #16 (from #7 in 2010) is partly attributed by the report authors to the improved performance of peers on pricing, public policy etc.

Bayer

Bayer's exposure to tropical diseases arises both from its Pharmaceuticals business, which is a key supplier of donated medicines for human African trypanosomiasis (sleeping sickness) and Chagas disease, and its CropScience business, which supplies insecticides as vector control agents. The company was a signatory of the London Declaration on NTDs and doubled its donations of treatments of Lampit (nifurtimox) for Chagas as part of its commitment to this initiative. As shown in Figure 45 it has a modest commercial exposure (>90% of its associated sales of just over €50m pa derive from its vector control agents) and its activities (drug donations, financial support, capacity building) are largely philanthropic in nature (it has provided its NTD drugs free of charge for over a decade and a current key project is to fund mobile intervention teams to deal with local outbreaks of human African trypanosomiasis in the heavily-affected Democratic Republic of Congo). Outside of NTDs, Bayer supplies the active ingredient of its antibiotic Avelox (moxifloxacin) at a reduced price for emergency use in multi-drug resistant TB.

Bayer's dedicated R&D spend for tropical diseases (at €3m in each business area) is small compared with other companies in our report and its key project within Pharmaceuticals is to develop a paediatric (smaller tablet) formulation of Lampit. It does not participate in WIPO Re:Search although it has granted open access to its molecular libraries for use in NTD R&D. Regarding vector control R&D, Bayer works with several academic institutions (London School of Tropical Medicine, Liverpool School of Hygiene and Tropical Medicines) and is a member of the Corporate Alliance on Malaria in Africa (CAMA). With regards to IP protection, the company is ranked below-average versus peers by the

Access to Medicine Index as Bayer files patents in Least Developed Countries (LDCs), unlike for example GSK, Novartis and Roche, and it does not commit to non-exclusive voluntary licences for its products. Bayer ranked #9 overall in the Access to Medicine Index 2012, up from #14 in 2010.

Figure 45: Bayer responses to Deutsche Bank tropical disease survey (edited by Deutsche Bank)

Question	Response
1. What is your company's sales exposure to tropical diseases?	Sales from pharma products against tropical diseases – Germanin, Lampit, Biltricide and Yomesan (detailed below) - were about €5m in 2013. Concerning vector control (= transmission control) for tropical diseases such as malaria, dengue fever and other insect transmitted tropical diseases, the sales in 2013 were approx. €46m.
2. Which are the key products that you supply either commercially or as donations to treat/prevent tropical diseases, either directly or via tender to bulk buying organisations (UNICEF/GAVI/PAHO etc)?	For HealthCare, our key products against tropical diseases are: (1) Lampit (nifurtimox used to treat diseases caused by trypanosomes including Chagas disease and sleeping sickness): WHO donation, Tender (Chile, Argentina), minimal private market; (2) Germanin (suramin for the treatment of sleeping sickness and onchocerciasis): WHO Donation, minimal private market; (3) Yomesan (niclosamin to treat tapeworms): private market; (4) Biltricide (praziquantel to treat flatworms): private market. In our vector-control business, the product range consists of insecticides to be sprayed inside the houses / huts (indoor residual spraying), the impregnation of mosquito nets, space spray formulations, and larvicides as main products. Commercially nearly 100% of these are sold via international competitive bidding/tenders to organizations like the Global Fund , USAID, WHO/PAHO, UNICEF, UNDP (to name a few).
3. Do you undertake tiered pricing in tropical diseases, given that the world's poorest nations often carry the main disease burden?	For HealthCare: Almost all patients receiving Lampit or Germanin in African sleeping sickness (HAT) and Chagas disease receive it via WHO donation. In HAT and Chagas disease the private market is minimal. Yomesan is only second-line treatment but under re-evaluation by WHO. Biltricide is sold in the private market. For vector control, as the quotes are going into the tender process with lowest price or best cost effectiveness requirements by the procuring organization we have no tiered pricing as such and the needed products are given free to the countries by the international community
4. Do you share access to your IP on drugs/vaccines for tropical diseases (please specify which therapy areas/drugs/vaccines if possible)?	Concerning HealthCare, all our established products suitable to fight NTDs are off-patent. In order to jointly develop new therapeutic approaches against NTDs, Bayer agreed to grant access to molecule libraries for identification of new molecules suitable for future therapies against NTDs. Concerning vector-control, there is no strict IP on insecticides in Public Health and WHO allows "equivalence" in their Pesticide Evaluation Scheme allowing generic companies to copy products of primary manufacturers. For impregnated bed nets (LifeNetTM) we are looking for local partners to produce the nets, e.g. in Africa for Africa.
5. What is your R&D spend on tropical diseases?	Approx. €3m was spent on R&D on tropical diseases (Chagas/Lampit) in 2013. Concerning vector-control, more than €3m per year (incl. contribution from the Bill & Melinda Gates Foundation) are spent on targeted research for new active ingredients for vector control.
6. Within your tropical disease R&D activities, which are the key projects, areas of focus and initiatives?	HealthCare is currently conducting adaptive R&D for Lampit in Chagas disease. This includes the development of a formulation suitable for children and more precise body weight adjusted treatment scheme as well as assessing a new dosage scheme for easier and shorter treatment. Key projects in vector control / transmission control are finding new molecules, new chemical classes to overcome and break insecticide resistance which is the biggest threat at the moment and for the future. In addition, we develop smarter formulations e.g. to have longer lasting activity to reduce re-spraying, or re-distribution of nets to increase value for money. For impregnated bed nets key areas are to find material which is stronger, softer and more durable in use.
7. Do you take active part in the wider provision of healthcare access in regions affected by tropical diseases (eg, nurse training)?	Being aware that besides drug donations, also financial support is needed to ensure the distribution of drugs and patients' access, Bayer annually supports the WHO with €300,000 for distribution and logistics of Lampit in Chagas disease since 2004. In 2013, Bayer has taken an innovative and unique in sector approach within the company's commitment to fight Chagas disease. A pilot model project was initiated in Argentina to increase awareness of patients for diagnosis and treatment of Chagas disease. As currently some 70% of all registered cases of HAT worldwide occur in the Democratic Republic of the Congo, we increased our commitment to the fight against African sleeping sickness in 2013, setting up a project for an initial term of three years during which we will provide €100,000 per year for the mobile intervention teams deployed by the WHO in DR Congo to tackle local outbreaks. With the help of these teams, people in remote areas are gaining better access to diagnosis and treatment. In addition, Bayer, together with other 18 German leading companies, has launched the AFRIKA KOMMT project to support local capability building and lay the foundation stone for sustainable economic cooperation with Africa. Bayer CropScience additionally provides training for the people who apply the products like the National Malaria Program spray teams and educate users on proper use of bed nets.

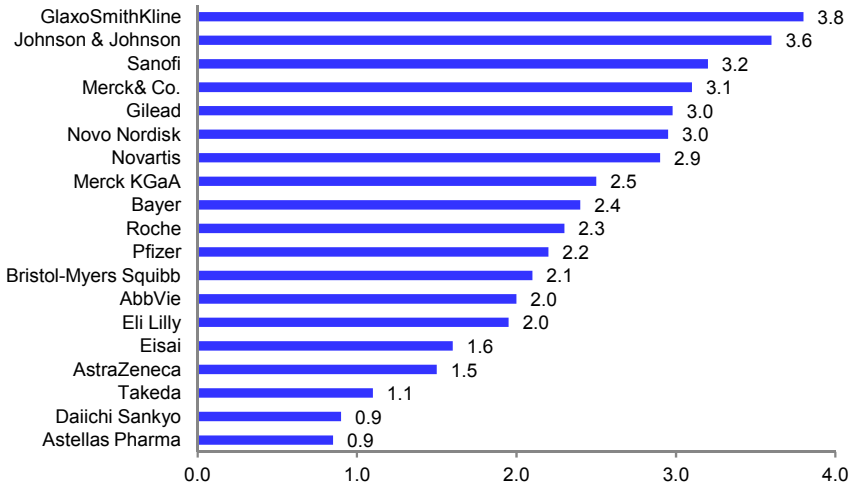
Source: Company data, Deutsche Bank

GlaxoSmithKline

GSK ranked #1 in the Access to Medicine Index 2012, maintaining its leading position of two years earlier (Figure 46). The company has a highly pro-active and innovative approach to healthcare access, pricing and patents, and the development of new medicines for the developing world, including for tropical diseases. It is consistently in the vanguard of industry efforts to address health issues for the poorest countries, eg, it was a signatory to the London Declaration on NTDs (at which its CEO, Sir Andrew Witty, spoke on behalf of the drug manufacturers) and was a founder of the WIPO Re:Search open-access database for neglected disease R&D.

In particular, however, we highlight GSK's pioneering Developing Countries and Market Access (DCMA) unit. Created in 2010, this is dedicated to expanding access to GSK's medicines and vaccines for the 800m people living in the 48 United Nations-designated Least Developed Countries (LDCs). To achieve this it has adopted a lower price/higher volume approach, with employees incentivized to increase volumes of product delivered rather than the bottom line. Attesting to the success of this initiative, GSK increased the volumes it delivered to the LDCs by 60% between 2010 and 2013 while capping its drug prices at 25% of those charged in developed countries - in some cases cutting prices by up to 50% (eg, on its antibiotic Augmentin). This approach is replicated in its market-leading vaccines business in which it caps pricing in LDCs at 25% of the average West European price (and has introduced price tiering based on GNP per capita, the lowest tier being equivalent to GAVI tender prices which can be 10% of those in the developed world). In addition to the foregoing, GSK commits to reinvest 20% of profits made in LDCs into projects that strengthen healthcare infrastructure and help widen access to medicines in the countries concerned. Most recently, GSK announced (in March 2014) a unique program of manufacturing and infrastructure investment in Africa (which augments its DCMA efforts as Africa includes 34 LDCs) to expand its local manufacturing capabilities, fund academic positions and train healthcare workers.

Figure 46: Rankings in the 2012 Access to Medicine Index



Source: Access to Medicine Index, 2012

Looking specifically at its tropical disease activities, GSK supplies a wide range of relevant products, including antibiotics, anti-parasitic drugs, anti-malarial drugs and anti-HIV/AIDS treatments (through its ViiV j/v). Key products for its vaccine business include Synflorix (pneumococcal vaccine), Rotarix (rotavirus), Cervarix (HPV) and combination vaccines for childhood diseases (DTP, hepatitis B, polio, measles, mumps, rubella). It does not disclose revenues in the area of tropical diseases but has confirmed to us that these are "minimal" in the specific area of NTDs. Here GSK has donated over 4bn albendazole treatments to the WHO to help control lymphatic filariasis (elephantiasis) and soil-transmitted helminthiases (intestinal worms) and has committed to supply a further 1bn tablets each year: 600m pa until lymphatic filariasis is eliminated and 400m pa for soil-transmitted helminthiases until 2020. At cost, GSK's donations (including other antibiotics etc) were valued at c.£150m in 2013.

In addition to ensuring that pricing is not an impediment to availability of its products in the poorer nations, GSK does not file patents or maintain existing patents in LDCs. In the specific area of HIV/AIDS, its ViiV j/v has a policy to grant non-royalty bearing voluntary licences to local generic companies in all low income, least developed and sub-Saharan African countries (138 in total). It has granted 18 such licences to date, including two (for paediatric abacavir and the recently-approved integrase inhibitor, dolutegravir) to the Medicines Patent Pool (MPP), the UN-backed IP-sharing organisation established in 2010 "*to improve access to appropriate, affordable HIV medicines and technologies for people living in developing countries*". The MPP makes available the IP to local generic companies in order to maintain supply of critically-needed drugs.

GSK's innovative approach to developing world issues, including tropical diseases, is also evident in its R&D activities. It has a dedicated Open Lab at Tres Cantos, Spain which focuses on diseases of the developing world and provides independent researchers with access to GSK facilities, resources and knowledge. This initiative will be replicated in a new Open Lab focused on non-communicable diseases in Africa as part of the previously-mentioned strategic investment in Africa. Currently GSK's researchers at Tres Cantos focus on developing drugs and vaccines for malaria, together with novel and adaptive approaches to visceral leishmaniasis, African trypanosomiasis (sleeping sickness) and Chagas disease (American trypanosomiasis). GSK also has work underway on potential dengue fever and Ebola vaccines although the former is at an early stage of development (its Ebola program has been accelerated given the devastating scale of the 2014 outbreak and its candidate vaccine has begun Phase I volunteer studies this month). GSK's highest profile program is the malaria vaccine RTS,S (or Mosquirix) which is soon to be filed with the regulators and may become the first approved *P. Falciparum* vaccine for use in infants and toddlers in sub-Saharan Africa. This vaccine, which was developed with support from PATH and the Bill & Melinda Gates Foundation, will be sold on a not-for-profit basis, assuming it gains the requisite approvals and WHO coverage. GSK also announced recently the entry into Phase III of tafenoquine, a drug with the potential to treat *P. Vivax* malaria (the strain predominantly found in SE Asia and LatAm). The malaria vaccine in particular has been very time-consuming (>20 years) and costly (>$350m) to develop and is, we believe, much the largest component of GSK's spend on R&D into NTDs (which has in recent years accounted for around a third of entire pharma industry spending on NTD R&D, averaging >$150m pa).

Figure 47: GSK responses to Deutsche Bank tropical disease survey (edited by Deutsche Bank)

Question	Response
1. What is your company's sales exposure to tropical diseases?	Not disclosed but "minimal" for products addressing NTDs (note: GSK has committed donations of albendazole, as detailed below). Developing Countries Unit sales are not disclosed.
2. Which are the key products that you supply either commercially or as donations to treat/prevent tropical diseases, either directly or via tender to bulk buying organisations (UNICEF/GAVI/PAHO etc)?	GSK supplies a wide range of products to treat and prevent tropical diseases given its long history in anti-infective drugs (originally through predecessor company Burroughs Wellcome), including anti-HIV/AIDS treatments through its ViiV j/v, and its leading position in the supply of vaccines to the developing world. In many countries GSK has adopted capped or tiered pricing of its commercially-available products to ensure the broadest possible access and in some cases (eg, HIV/AIDS) it does not enforce its IP rights, thereby allowing low-cost local generic manufacture of critically-needed drugs. Key anti-infective drugs include the antibiotics Augmentin and Zinnat. As regards vaccines, over 80% of GSK's 862m vaccine doses in 2013 were delivered to the developing world and here key products include Synflorix (pneumococcal vaccine), Rotarix (rotavirus vaccine), Cervarix (HPV vaccine) – where GSK has also made GAVI commitments – as well as a range of combination vaccines for common childhood diseases (diphtheria, typhoid, pertussis, hepatitis B, polio, measles, mumps, rubella). In terms of donations, GSK has supplied over 4bn albendazole treatments to help control lymphatic filariasis (elephantiasis) and soil-transmitted helminthiases (intestinal worms). It has committed to supply 1bn tablets of albendazole each year: 600m pa until lymphatic filariasis is eliminated and 400m pa for soil-transmitted helminthiases until 2020. In total its donations (including other antibiotics etc) were valued at £146m in 2013 at cost price (£512m at WAC).
3. Do you undertake tiered pricing in tropical diseases, given that the world's poorest nations often carry the main disease burden?	As stated, GSK routinely uses tiered or capped pricing in developing countries via its flexible pricing strategy and innovative business model approach. Its unique Developing Countries and Market Access (DCMA) unit has a target of increasing access to the 800m living in least developed countries (LDCs), adopting a lower price/higher volume approach. To achieve this it has capped pricing at 25% of those charged in developed countries and cut prices substantially (eg, by up to 50% on its key antibiotics) in order to stimulate greater volumes. Sales representatives are incentivized by volumes rather than bottom-line contribution. As a consequence GSK's volumes in LDCs have expanded by 60% since 2010. GSK has employed tiered pricing in vaccines for over 20 years (the lowest tier countries receive the same prices as GSK supplies to the GAVI alliance and can be as low as 10% of developed world prices;. GSK has also frozen prices for developing countries graduating from GAVI for 5 years). For its malaria vaccine candidate RTS,S GSK has committed that price will not be a barrier to access and the eventual price will cover cost of the vaccine with small return of c.5% which will be reinvested in R&D for 2nd generation malaria vaccines or other NTD vaccines.
4. Do you share access to your IP on drugs/vaccines for tropical diseases (please specify which therapy areas/drugs/vaccines if possible)?	GSK has a number of approaches to ensuring that IP does not represent an impediment to access to its products and R&D activities in NTDs. These include, for example: granting 18 non-royalty bearing voluntary licences for the range of HIV drugs produced by its ViiV j/v (including recently approved dolutegravir) to the Medicines Patent Pool (MPP). Its open innovation approach includes being more open with IP as a founding member of WIPO Re:Search, researching and developing new drugs at its dedicated developing world R&D facility at Tres Cantos, Spain; its Open Lab approach (giving access to independent researchers to GSK facilities, resource and knowledge at both Tres Cantos and new open lab focused on NCDs in Africa) ; and its contribution of multiple '000 screened compounds with activity against malaria and TB to public researchers (also now screening for visceral leishmaniasis).
5. What is your R&D spend on tropical diseases?	While GSK does not routinely disclose this figure, the Access to Medicine Index 2012 notes that the company spent $338m on R&D into NTDs over the two-year (2010-2011) Index period (ie, averaging $169m pa). Based on R&D funding data from G-FINDER, GSK accounted for close to one-third of overall pharma industry R&D spend on NTDs and over 5% of global R&D spend on NTDs. GSK has invested more than $350m in development of its malaria vaccine candidate RTS,S – developed in partnership with PATH MVI, supported by grants from the Bill & Melinda Gates Foundation.
6. Within your tropical disease R&D activities, which are the key projects, areas of focus and initiatives?	GSK's highest profile program is the malaria vaccine RTS,S (or Mosquirix) which is shortly to be filed with the regulators and may become the first approved *P. Falciparum* malaria vaccine for use in infants and toddlers, mainly in sub-Saharan Africa. GSK also announced recently the entry into Phase III of tafenoquine, a drug with the potential to treat *P. Vivax* malaria (the strain predominantly found in SE Asia and LatAm). In addition, its researchers at Tres Cantos are investigating novel and adaptive approaches to visceral leishmaniasis, African trypanosomiasis (sleeping sickness) and Chagas disease (American trypanosomiasis). It is also collaborating with FioCruz in Brazil and the Walter Reed Institute on a potential dengue fever vaccine and has a vaccine program in Ebola.
7. Do you take active part in the wider provision of healthcare access in regions affected by tropical diseases (eg, nurse training)?	The company believes that strengthening healthcare systems is key to improving the lives of those living with or at-risk of tropical diseases (and other diseases of poverty). It has multiple programs across the developing world to help develop healthcare infrastructure, improve sanitation and increase education and training in health-related matters. Two unique programs relate to its LDC initiative and a recently-announced strategic investment in Africa. As regards its LDC initiative, GSK has committed to reinvest 20% of profits generated in those countries into community programs (eg, training health workers and building capacity through support and infrastructure). This reinvestment amounted to £5.1m in 2013 (based on 2012 profits) and a total of £15m since 2009. In March 2014, GSK announced an unprecedented £130m investment program in Africa, which will lead to the creation of a dedicated Open Lab to increase understanding of NCD variations seen in Africa, helping to inform prevention and treatment strategies. Other elements of this strategic investment program in Africa include expansion of local manufacturing capacity in Nigeria and Kenya, building up to 5 new manufacturing sites, funding 25 academic Chairs at African universities and a commitment to train an additional 10,000 community workers. New healthcare delivery models are being developed with OneFamilyHealth (franchise system for nurses to own and operate clinics in Rwanda and Kenya), and partnerships with Barclays (to increase access to affordable healthcare in Zambia) and Vodafone (using mobile tech to increase vaccination rates in Mozambique).

Source: Company data, Deutsche Bank

Novartis

Novartis' outstanding contribution to the fight against tropical disease is its industry-leading effort in the provision of malaria treatment and support, based largely around its key combination therapy Coartem (detailed below). It also supplies a range of other relevant products including vaccines for rabies (Rabipur, Rabavert) and other infectious diseases of the tropics (eg, for typhoid and parathyroid fever), and generic rifampicin-based treatments for TB (the latter through its Sandoz subsidiary). In the area of NTDs, Novartis has major ongoing donations of multi-drug therapy (rifampicin/clofamazine/dapsone) for leprosy (where it is responsible for almost 100% of the annual supply to the WHO) and of the anti-fluke drug triclabendazole for fascioliasis and paragonimiasis. Novartis was a signatory of the London declaration on NTDs and extended its leprosy donation program (which includes unlimited quantities of drug) as a sign of its commitment. For a number of these products Novartis offers on-the-ground support and capacity-building programs (eg, it operates a TB surveillance program in Tanzania to help monitor disease transmission while the Novartis Foundation for Sustainable Development supports global efforts at leprosy diagnosis and treatment). Novartis does not disclose its revenues from such activities but these are likely to be very modest given their largely philanthropic nature. Consistent with this, Novartis operates tiered pricing structures for the private, middle-income and public/tender markets and it does not file or maintain patents in LDCs and several other low- or low/middle-income countries (LICs, LMICs). Its broad-ranging efforts and dedicated R&D activities (discussed below) led it to attain the #7 ranking in the Access to Medicine Index 2012 (while down from #3 in 2010, the gap in scores between #3 and #7 was relatively small; Figure 46).

Novartis is the largest supplier of artemisin-based combination anti-malarial therapies (ACTs) to the WHO and has provided more than 600m treatment courses free of charge since 2001. Coartem was the first ACT to be included in the WHO's Model List of Essential Medicines (in 2002) and accounts for more than three-quarters of all ACTs delivered. Building on this, Novartis was able to develop and launch the first paediatric ACT (Coartem Dispersible) in 2009 and has since supplied over 200m tablets of this child-friendly anti-malarial combination to 40 countries, mostly in Africa. As an example of its continuing efforts to help control the disease, in April 2014 Novartis announced the delivery of 2m Coartem Dispersible tablets to Zambia in conjunction with Malaria No More's 'Power of One' campaign. This new campaign is sponsored by Novartis and matches public donations with donations from the company (in this case 1m apiece). Novartis coordinates its activities in this disease area, including the provision of on–the-ground-infrastructure, medical training etc, through the Novartis Malaria Initiative (Figure 38), which it believes to be one of the largest access-to-medicine programs in the healthcare industry. One of its groundbreaking programs is 'SMS for Life' which employs mobile phone technology to monitor stocks of anti-malarial drugs in distribution depots and pharmacies in order to minimize stock-outs in the event of disease outbreaks.

Novartis has two dedicated R&D units, namely the Singapore-based Novartis Institute for Tropical Diseases (NITD) and the Novartis Vaccines Institute for Global Health (NVGH; which is based in Siena, Italy and will transfer to GSK on its acquisition of Novartis' vaccines business). These two units spent $18m and $9m respectively in 2013 on researching and developing affordable new medicines and vaccines for the developing world on a not-for-profit basis. In–

line with Novartis' leading position in the provision of malaria treatment, the NITD's main projects are targeted against this disease, although it also researches medicines for dengue, African trypanosomiasis and diarrheal disease. Key programs include a new formulation of Coartem with a reduced pill burden (requiring 6, as opposed to 24 pills) and two novel Phase II anti-malarials, KAE609 and KAF156, each of which could potentially act as a single-dose cure. In August 2014, the NITD licensed its TB R&D program (including a portfolio of pre-clinical compounds) to the Global Alliance for TB Drug Development. Consistent with its not-for-profit approach, Novartis was a founding member of the WIPO Re:Search database consortium for neglected infectious diseases and contributes primary screening and medicinal chemistry data to the ChEMBL - Neglected Tropical Disease Archive (ChEMBL-NTD).

Figure 48: Novartis responses to Deutsche Bank tropical disease survey (edited by Deutsche Bank)

Question	Response
1. What is your company's sales exposure to tropical diseases?	Exact sales not disclosed but in 2013 63% of Novartis Pharma's sales in sub-Saharan Africa (ex S. Africa) derived from Coartem. Also Novartis delivered 7.5m rabies vaccine (Rabipur/Rabavert) doses of which Rabipur accounted for 95% in Index Countries (defined by Access to Medicine Foundation)
2. Which are the key products that you supply either commercially or as donations to treat/prevent tropical diseases, either directly or via tender to bulk buying organisations (UNICEF/GAVI/PAHO etc)?	For malaria, Novartis supplies the artemisin-based combination (ACT) drug Coartem without profit for public sector use. It has donated more than 600m tablets to date and has multiple donation programs in Africa (eg, for the Millennium Villages Project in Tanzania, for Sudanese refugees and, most recently, via the Power of One donation-matching campaign together with Malaria No More). In the area of NTDs, Novartis has donated over 2.3m tablets of Egaten (triclabendazole) via the WHO for mass administration against fascioliasis and pargonimisasis (valued at c.$1m), helping to cure more than 1.15m patients. For leprosy, Novartis supplies the multi-drug therapy combination free of charge to the WHO and expects to treat 850,000 people through the year 2020 (valued at c.$25m)
3. Do you undertake tiered pricing in tropical diseases, given that the world's poorest nations often carry the main disease burden?	Novartis operates three-tier pricing for Coartem: the first tier applies to the public sector and NGOs (Coartem and Coartem Dispersible treatments are delivered without profit); the second tier applies to the non-premium private sector and applies highly subsidized pricing through participation in the Global Fund's Affordable Medicines Facility for Malaria (AMFm) initiative; the third tier applies to the premium (for-profit) private sector. For rabies vaccines, pricing is determined through competitive tenders to UNICEF and other organizations. Novartis' aim to deliver accessible and affordable vaccines that address unmet medical need in endemic regions has resulted in a development and licensing agreement for two typhoid and paratyphoid fever vaccines with India's Biological E Limited (BioE).
4. Do you share access to your IP on drugs/vaccines for tropical diseases (please specify which therapy areas/drugs/vaccines if possible)?	Novartis' policy is not to file or maintain patents in any of the 48 Least Developed Countries (LDCs) designated by the UN and this principle is replicated in several low- and low/middle-income (LIC, LMIC) countries outside of the officially designated LDCs
5. What is your R&D spend on tropical diseases?)	Novartis Institute for Tropical Diseases (NITD) spent $17.8m on R&D in 2013, while the Novartis Vaccines Institute for Global Health spent $8.8m
6. Within your tropical disease R&D activities, which are the key projects, areas of focus and initiatives?	Novartis' key project is a new formulation of the anti-malarial Coartem (Coartem 80/480) which aims to reduce the pill-burden from 24 to 6 pills. Elsewhere Novartis is developing a new formulation of the mosquito control agent Altosid and has two novel drugs in Phase II for malaria, the spiroindolone KAE609 (which has been shown to kill the blood stage of *P. falciparum* and *P. vivax*) and the imidazolopiperazine: KAF156 (which may act on both the blood and liver infection stages). Novartis participates in a number of R&D initiatives/programs dedicated towards tropical diseases. For example it was a founding member of the World Intellectual Property Organization (WIPO) Re:Search Consortium, which was established to accelerate discovery and development of medicines, vaccines and diagnostics for neglected infectious diseases, notably malaria and TB, via a public database of available IP assets (it contains information on individual compounds and associated data, screening hits from compound libraries and clinical trial data). Novartis also contributes to ChEMBL - Neglected Tropical Disease Archive (ChEMBL-NTD), an open-access archive of primary screening and medicinal chemistry data directed at neglected diseases, including tropical diseases. Elsewhere, Novartis participates in the Ifakara Health Institute (IHI) TB Collaboration in Tanzania which aims to develop a comprehensive molecular tool for large-scale surveillance of resistant TB and to establish a TB genotyping center of excellence to track disease transmission, with the ultimate goal of better managing/controlling the disease. Its NITD R&D unit has a collaboration in malaria and TB research with H3D, the first and only drug discovery and development centre in Africa (affiliated with the University of Cape Town). In Asia, NITD collaborates with Hasanuddin University on epidemiology research in TB and the development of diagnostic kits for dengue fever.
7. Do you take active part in the wider provision of healthcare access in regions affected by tropical diseases (eg, nurse training)?	Novartis convenes meetings with managers of National Malaria Control Programs (NMCP) in Africa each year, designed to share best practice and experiences, highlight successes and challenges, and discuss solutions. From these meetings, Novartis designs and implements groundbreaking projects including packaging changes for its anti-malarial treatment, making transport and storage more efficient; as well as the SMS for Life program to solve the issue of stock outs and stock management

Source: Company data, Deutsche Bank

Roche

Unlike the other companies surveyed here, Roche was not a signatory of the London Declaration on NTDs, reflecting its lack of specific focus on tropical diseases. It does, however, supply a range of pharmaceutical and diagnostic products and services and engage in healthcare capacity building programs to help in the fight against NTDs and other diseases endemic in the tropics. These activities – particularly its flexible pricing in HIV/AIDS - supported its #10 overall ranking in the Access to Medicine Index 2012 (which represented slight slippage from #6 in 2010). In terms of NTDs, Roche supplies the off-patent Radanil/Rochagan (benznidazole) to treat Chagas disease. While it does not make individual product donations, it handed over the technical and production know-how for benznidazole to the Brazilian government in 2008. Beyond NTDs, Roche supplies the malaria medicines Lariam (mefloquine) and Fansidar (sulfadoxin + pyrimethamine), along with a range of anti-infective drugs (eg, the antibiotics Rocephin and Bactrim), TB drug Rimifon (isoniazid) and HIV treatment Invirase (saquinavir). In total Roche supplies 24 drugs included in the WHO's essential medicines list (which numbers around 350 medicines). Its IP position is also highly supportive as Roche does not file for new patents or enforce existing patents in LDCs or low-income countries.

Roche's activities in the HIV/AIDS field are particularly worthy of note (while HIV/AIDS is not a tropical disease *per se*, two-thirds of the 35m people infected globally are in Sub-Saharan Africa). Here the company supplies the protease inhibitor Invirase (saquinavir) at a no-profit price to LDCs and to sub-Saharan Africa. In 2013, it additionally began to supply Valcyte (for AIDS-related cytomegalovirus infections) through the Medicines Patent Pool to non-governmental organizations at ultra-low pricing (making the cost 90% cheaper in 138 developing countries). It supports access to its HIV medicines in sub-Saharan African countries by not filing or enforcing patents so that locally manufactured generics can be freely produced. It built upon this by a Technology Transfer Initiative (considered unique in the sector by the Access to Medicine Foundation) which assisted 13 local manufacturers (12 based in Africa, 1 in Bangladesh) in establishing production of saquinavir over 2006-2010. This initiative included providing guidance on technical aspects of manufacturing, on-site training, seminars in Good Manufacturing Practice (GMP) etc. Its philanthropic activities in HIV/AIDS are mirrored by its diagnostics business which has a long-running program (AmpliCare) in sub-Saharan Africa and certain other endemic parts of the world (LatAm, Asia) to build and equip laboratories (eg, the Roche Scientific Campus in Johannesburg, South Africa), to train health workers and to diagnose and monitor HIV/AIDS patients.

Roche's activities with regard to tropical diseases, while highly laudable, largely reflect its historic portfolio of anti-infective medicines and we are not aware that it currently has pro-active R&D activities in this field (its published new drug pipeline does not list any relevant projects although the company states that it focuses on serious and life-threatening diseases, no matter where they predominate). It does not disclose its spend in this regard but we assume it is very modest, at no more than $10m pa. We also note that Roche does not contribute to WIPO Re:Search, the database for R&D into NTDs, although it has made its chemical libraries available to OneWorld Health (part of the international not-for-profit PATH organization) and in 2003 it donated two molecules to the Medicines for Malaria Venture (of which OZ439 is currently in Phase II trials in combination with Sanofi's putative anti-malarial ferroquine).

Figure 49: Roche responses to Deutsche Bank tropical disease survey (edited by Deutsche Bank)

Question	Response
1. What is your company's sales exposure to tropical diseases?	Not disclosed.
2. Which are the key products that you supply either commercially or as donations to treat/prevent tropical diseases, either directly or via tender to bulk buying organisations (UNICEF/GAVI/PAHO etc)?	Key products are as follows: for Chagas disease, Radanil and Rochagan (benznidazole); for malaria, Lariam (mefloquine) and Fansidar (sulfadoxin + pyrimethamine); for dengue, a molecular diagnostic test. In addition Roche supplies the broad use (non-specific) anti-infectives Rocephin (ceftriaxone; broad spectrum cephalosporin antibiotic), Bactrim (sulfamethoxazole; anti-bacterial agent) and Ancotil (flucytosine; anti-fungal) Roche don't provide donations as such, although on occasion we have donated benznidazole for treating Chagas. Instead we donated the rights, trade data and knowledge and technical information to manufacture benzonidazole to the Brazilian government (see full notes below).
3. Do you undertake tiered pricing in tropical diseases, given that the world's poorest nations often carry the main disease burden?	To provide sustainable access to Roche products in emerging and developing countries, Roche applies inter- and intra-country differential pricing, if reasonable and feasible from a global/local business, regulatory, legal and infrastructural perspective. We offer flexible pricing in all middle and low income countries, for a number of our products in the areas of oncology, viral hepatitis, influenza, HIV/AIDS and rheumatoid arthritis.
4. Do you share access to your IP on drugs/vaccines for tropical diseases (please specify which therapy areas/drugs/vaccines if possible)?	In 2003 Roche donated the molecule known as OZ277 as well as the second generation OZ439 (both in pre-clinical development) to the Medicines for Malaria Venture (MMV) for their development. In addition, we opened our chemical library to them for screening for any additional compounds and provided expertise in both clinical drug development and specifically in malaria drug development. This partnership has resulted in two new anti-malarials available on the market (not marketed by Roche).See www.mmv.org/newsroom/press-releases/roche-hands-over-ranbaxy Roche opened its chemical library to the Institute for OneWorld Health for them to screen for neglected disease targets and support their R&D efforts to find a medicine to treat diarrhea, a leading cause of mortality in children under five years of age in developing countries. Any compounds identified were donated to them. In December 2011, OneWorld Health became a drug development program of PATH, an international nonprofit organization that transforms global health through innovation. Since then the programs are on hold. To assist Brazil's efforts to reduce the impact of Chagas disease, Roche donated the rights, trade data and knowledge and technical information to manufacture its medicine benznidazole to the Brazilian government. The technical transfer was completed in 2008. Following Roche's donation, the Brazilian government set up a manufacturing plant in the state of Acre (Amazon region) and started producing the finished drug with the know-how supplied by Roche. The organization manufacturing benznidazole is now known as the State Pharmaceutical Laboratory of Pernambuco (LAFEPE). Nortec Quimica is producing the active pharmaceutical ingredient. LAFEPE has received pre-qualification to export the medicine to comply with worldwide demand. The product is exported by an international distributor upon request. We recognise that flexibility around patents in some of the poorest countries can help broaden access to medicines. For that reason, we do not file for new patents or enforce existing patents in least developed countries (LDCs), as defined by the United Nations, or in low-income countries (LICs), as defined by the World Bank. We also do not file or enforce patents for any antiretroviral HIV medicines in sub-Saharan African countries, where HIV/AIDS affects over 22.5 million people. Not applying patents in these regions enables generic versions of any Roche medicine to be produced and distributed in these countries without applying for a license. In addition, through our Technology Transfer Initiative we also help manufacturers in these countries to produce generic versions of our products.
5. What is your R&D spend on tropical diseases?	Spend not disclosed but Roche focuses R&D expertise on the search for differentiated and innovative new medicines as well as diagnostics. The focus is on serious and life-threatening diseases where the greatest difference can be made to addressing unmet medical needs, no matter where they predominate. We do not have a focus on tropical diseases but on where we can make a value-added product, irrespective of the disease.
6. Within your tropical disease R&D activities, which are the key projects, areas of focus and initiatives?	Not disclosed
7. Do you take active part in the wider provision of healthcare access in regions affected by tropical diseases (eg, nurse training)?	Yes, we spend considerable resources in helping build and strengthen local healthcare infrastructure. We have multiple types of programs in each country, in partnership with local stakeholders, based on their local needs. Examples of such programs can be found on our Access website www.roche.com/access_to_healthcare and www.roche.com/making_innovation_accessible.

Source: Company data, Deutsche Bank

Sanofi

Sanofi ranked highly in the Access to Medicine Index 2012, moving up two places to #3 (Figure 46). Like its peers GSK and Novartis, the company plays a central role in the provision of drugs and vaccines for tropical diseases and – consistent with its overall industry leadership position in EMs (Annex 2) – it maintains a pro-active approach to expanding healthcare access in the developing world. Thus Sanofi was a founder of the WIPO Re:Search consortium for neglected disease R&D in 2011 and a signatory to the London Declaration on NTDs in 2012. Furthermore its dedicated Access to Medicines department is tasked with developing innovative local access initiatives and has a direct reporting line (via the Senior VP of CSR) to Sanofi's CEO, Chris Viehbacher. Separately, its CEO and Chairman are members of the Board of the Sanofi Espoir Foundation, an award-winning organisation which aims to reduce health inequalities via development aid projects and responses to humanitarian emergencies. In total, Sanofi operates 260 access to healthcare programs in 70 countries, benefiting an estimated 177m people globally.

Sanofi has partnered with the WHO since 2001 in the area of NTDs, initially supplying several anti-infective drugs (eflornithine, melasoprol, pentamidine) free-of-charge to treat Human African Trypanosomiasis (sleeping sickness). The Access to Medicine Foundation notes that this program has saved more than 150,000 lives. Between 2006 and 2010 this partnership was expanded to include donation programs for three additional NTDs (leishmaniasis, Buruli ulcer and Chagas disease). Subsequently Sanofi extended the supply of unlimited quantities of the aforementioned drugs from 2016 to 2020 as part of its commitment to the London Declaration on NTDs (it also committed to manufacture 120m tablets of diethylcarbamazine over 2012-2013, in partnership with Eisai and the Bill & Melinda Gates Foundation, with the aim of treating 30m people with lymphatic filariasis). In the field of malaria, Sanofi began the large-scale manufacture (in April 2013) of semi-synthetic artemisinin (the key ingredient of ACTs, usually sourced from the sweet wormwood plant), together with PATH's Drug Development Program. This will supply sufficient raw material for up to 125m ACT treatments annually on a no-profit/loss basis.

Outside its donation programs, Sanofi markets a number of tropical disease drugs, including the artemisin-based combination anti-malarial AS-AQ and the leishmaniasis drug Glucantime (meglumine antimoniate). It operates a tiered pricing system for these, with ultra-low prices in developing countries (eg, AS-AQ is supplied to children and infants in public markets at just 50c). Importantly Sanofi supplies the broadest range of vaccines for diseases of the developing world (eg, yellow fever, cholera, DTP, tetanus, typhoid and rabies). We note that Sanofi's vaccines subsidiary Sanofi Pasteur is the joint industry leader (with GSK) in the supply of vaccines to EMs (Annex 3) and that it sells its vaccines to GAVI at the lowest prices worldwide for eligible countries. The majority of the >1bn doses it supplies are destined for the developing world.

In terms of patents, Sanofi's policies are similar to the best practice of peers such as GSK. It does not file or enforce patents in LDCs and other low-income countries and has committed to waive its patents (eg, on AS-AQ) in emergency or serious public health situations. Sanofi does not have a policy for non-exclusive voluntary licencing (this tends to be seen with those supplying HIV/AIDS medications in which Sanofi does not have a presence). However it considers such licences on a case-by-case basis where the need is high.

In many cases, Sanofi's R&D in the field of tropical diseases is philanthropic in nature. For example it has a collaboration with the Drugs for Neglected Diseases Initiative (DNDi) under which any resulting new drugs for Human African Trypanosomiasis, leishmaniasis or Chagas will be made available on a royalty-free basis to all developing countries. It also has R&D partnerships with MMV (with which it is developing a novel anti-malarial, ferroquine, in Phase II) and PATH (Institute for OneWorld Health) and is collaborating in Argentina to develop an oral vaccine for Chagas. Its highest profile product for tropical diseases, however, is its dengue fever vaccine (CYD TDV). Results from the second pivotal Phase III study on this vaccine were recently reported and, given their consistency with the positive findings from the first trial (with c.60% efficacy and major public health benefits), could support launches in the coming 1-2 years. Sanofi will make this vaccine available with tiered pricing but nevertheless predicts that the market for such a vaccine could reach €1bn pa which – given that competition appears years way – implies that its dengue vaccine could be most commercially successful vaccine ever in the developing world. Its optimism is based on the exceptional public health threat of dengue and resulting strong demand for a vaccine (with health economists modeling demand running to billions of doses). Sanofi does not disclose its R&D spend on tropical diseases but its CSR report mentions €30m of R&D investment "to fight malaria, tuberculosis, and leishmaniasis, including vaccines". Adding in likely spend on the dengue vaccine, we tentatively estimate that Sanofi spent around $100m on tropical disease R&D in 2013, putting it second only to GSK.

Figure 50: Sanofi responses to Deutsche Bank tropical disease survey (edited by Deutsche Bank)

Question	Response
1. What is your company's sales exposure to tropical diseases?	Less than 1% of overall sales (where tropical diseases are defined as the 17 NTDs plus malaria), but 28% of sales in sub Saharan Africa (ie, Africa, excluding North Africa and South Africa).
2. Which are the key products that you supply either commercially or as donations to treat/prevent tropical diseases, either directly or via tender to bulk buying organisations (UNICEF/GAVI/PAHO etc)?	Regarding donations, Sanofi has since 2001 supplied eflornithine, pentamidine and melarsoprol to the WHO for the treatment of sleeping sickness (Human African Trypanosomiasis; HAT). In addition, it has supplied financial support to support national HAT programs, ensuring treatment is free for the patient. Over 2001-2016, the value of the program is estimated at $75m. As regards commercial sales, Sanofi supplies the anti-malarial combination, artesunate-amodiaquine (AS-AQ), mainly to the Global Fund and the President's Malaria Initiative (PMI). It also supplies Glucantime (meglumine antimoniate) for leishmaniasis, with a large proportion of LatAm sales via PAHO, and the rabies vaccine Verorab (over the past 20 years, nearly 20m people in 100 countries have been treated against rabies with Sanofi Pasteur vaccines and immunoglobulins). Beyond rabies, Sanofi Pasteur supplies the broadest range of vaccines for travelers, the military, and populations living in tropical areas. Its portfolio includes vaccines for cholera, diphtheria, tetanus, hepatitis A and B, Japanese encephalitis, meningococcal diseases, typhoid, and yellow fever. Sanofi Pasteur has been the primary supplier of yellow fever vaccine for Africa for 60 years (supplying over 200m doses in the past 20 years). Sanofi Pasteur has provided 6m doses of vaccine for the stockpile funded by GAVI for routine immunization and to control yellow fever outbreaks in Africa (re-emergence of yellow fever results in c.200,000 cases and 30,000 deaths every year). In September 2013 Sanofi Pasteur announced plans to significantly increase its Stamaril yellow fever vaccine capacity at its facility in Val de Reuil, France (Stamaril was pre-qualified by the WHO in 1987 and is marketed in over 70 countries). Elsewhere, Sanofi Pasteur received the first WHO pre-qualification for a typhoid fever vaccine in 2011, while its Indian subsidiary Shantha received WHO pre-qualification for its oral polio vaccine the same year (this is now procured to UN Agencies).
3. Do you undertake tiered pricing in tropical diseases, given that the world's poorest nations often carry the main disease burden?	Sanofi has tiered pricing in place for Glucantime, charging $1.2/ampoule (plus transport/taxes) for all developing countries for public markets. Regarding its anti-malarial combination AS-AQ, this has had dual public/private market pricing since launch (the public price has always been $1 for treatment [3 days] for adults, and $0.5 for children and infants). For Verorab, Sanofi Pasteur supplies large quantities for public and/or private markets depending on the market structure and maturity. Public markets comprise government tenders for nationwide immunization programs, while prices in the private segment are adapted to the upper-middle class population's ability-to-pay in a given country.
4. Do you share access to your IP on drugs/vaccines for tropical diseases (please specify which therapy areas/drugs/vaccines if possible)?	Sanofi signed an agreement with the Drugs for Neglected Diseases Initiative (DNDi) in 2010 whereby any developments undertaken with DNDi in the field of HAT, leishmaniasis or Chagas disease which result in a new drug will be made available on a royalty free basis to all developing countries.
5. What is your R&D spend on tropical diseases?	Not disclosed but company's 2013 CSR report mentions "€30m invested in research and development to fight malaria, tuberculosis, and leishmaniasis, including vaccines." This amount does not include spend on the dengue vaccine, we believe.
6. Within your tropical disease R&D activities, which are the key projects, areas of focus and initiatives?	The highest profile project is the dengue fever vaccine (CYD TDV) under development by Sanofi Pasteur. In total the company has invested over €1bn towards development of dengue vaccine over more than two decades (including >€300m on a dedicated production plant in Lyon, France). The first of two large pivotal Phase III trials was reported in April 2014 and showed a 56.5% efficacy rate, together with substantial reductions in dengue hospitalizations and cases of dengue haemorrhagic fever. The second Phase III trial reported headline data in September 2014, showing 60.8% efficacy and reductions in hospitalizations and severe dengue cases consistent with the first trial. Elsewhere in the field of NTDs, Sanofi is collaborating with the Malaria Medicines Venture (MMV) on a new non-artemisinin based combination treatment, OZ439/ferroquine, which is in Phase II testing for non–complicated malaria (ferroquine is the Sanofi compound, while OZ439 was donated to MMV by Roche). In HAT, Sanofi is co-developing a new oral treatment, fexinidazole, together with DNDi. If ongoing Phase III trials are successful, fexinidazole will be submitted to the EMA for an Article 58 approval next year (note: fexinidazole is a former-Hoechst product which Sanofi has the responsibility to manufacture, register and supply at an accessible price, including donation to the WHO. This drug is also being investigated with DNDi in visceral leishmaniasis and Chagas. Finally Sanofi is developing a topical meglumine gel for cutaneous leishmaniasis (Phase II to start in 2015).
7. Do you take active part in the wider provision of healthcare access in regions affected by tropical diseases (eg, nurse training)?	For malaria, the Access to Medicines department has a range of educational activities, for health workers (annual symposium for Malaria program directors, educational material), the public (School children against Malaria theatre groups, Mosquikit educational game, storyboards), and those involved in the supply chain (training courses). For leishmaniasis, Sanofi supplies a manual for health workers, training CDs in LatAm and educational booklets for children. For HAT, it supplies 'reminder posters' in health centres. For rabies, Sanofi Pasteur has hosted disease master classes in Pakistan.

Source: Company data, Deutsche Bank

Annex 1: The tropics

The tropical zone is generally defined as that part of the world situated between the Tropics of Cancer and Capricorn. It contains 144 countries, including 43 of the UN's list of 48 Least Developed Countries (LDCs).

Figure 51: Countries/nations within the tropics (italicised = only partly within; shaded = UN-designated LDC)

Central & Southern Africa	Northern Africa & Middle East	Oceania	South East Asia, incl. China
Algeria	Djibouti	American Samoa (United States)	Brunei
Angola	Chad	*Australia*	Cambodia
Benin	Eritrea	Cook Islands	*China*
Botswana	*Mali*	Fiji	China – Hong Kong SAR
Burkina Faso	*Mauritania*	French Polynesia	China – Macau SAR
Burundi	Niger	Guam (US)	Indonesia
Cameroon	*Oman*	Kiribati	Laos
Cape Verde	*Saudi Arabia*	Marshall Islands	Malaysia
Central African Republic	Senegal	Micronesia, Federated States of	*Myanmar*
Comoros	Somalia	Midway Islands (US)	Philippines
Congo, Democratic Republic of	South Sudan	Nauru	Singapore
Congo, Republic	Sudan	New Caledonia (France)	*Taiwan*
Cote d'Ivoire	*United Arab Emirates*	Niue	Thailand
Egypt	Yemen	Northern Mariana Islands (US)	Timor-Leste
Equatorial Guinea		Palau, Republic of	Vietnam
Ethiopia	**Caribbean**	Papua New Guinea	
Gabon	Anguilla (UK)	Samoa	**Central America**
Gambia	Antigua and Barbuda	Solomon Islands	Belize
Ghana	Aruba (Netherlands)	Tokelau	Costa Rica
Guinea	*Bahamas*	Tonga	El Salvador
Guinea-Bissau	Barbados	Tuvalu	Guatemala
Kenya	British Virgin Islands (UK)	*United States (Hawaii)*	Honduras
Liberia	Cayman Islands (UK)	Vanuatu	*Mexico*
Libya	Cuba	Wake Island (US)	Nicaragua
Madagascar	Dominica	Wallis & Futuna Islands (France)	Panama
Malawi	Dominican Republic		
Mauritius	Grenada	**South Asia**	**South America**
Mayotte (France)	Guadeloupe (France)	*Bangladesh*	*Argentina*
Mozambique	Haiti	*India*	Bolivia
Namibia	Jamaica	Maldives	*Brazil*
Nigeria	Martinique (France)	Sri Lanka	*Chile*
Reunion (France)	Montserrat (UK)		Colombia
Rwanda	Netherlands Antilles (Netherlands)		Ecuador
Sao Tome & Principe	Puerto Rico (US)		French Guiana (France)
Seychelles	Saint Kitts & Nevis		Guyana
Sierra Leone	Saint Lucia		*Paraguay*
South Africa	St Vincent & the Grenadines		Peru
Tanzania	Trinidad and Tobago		Suriname
Togo	Turks & Caicos Islands (UK)		Venezuela
Uganda	United States Virgin Islands (US)		
Zambia			
Zimbabwe			

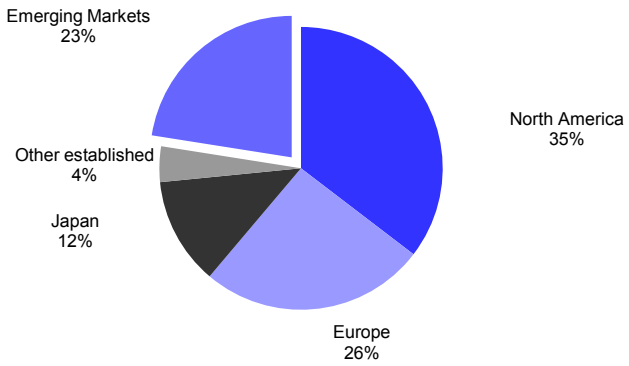
Source: State of the Tropics website; Deutsche Bank

Annex 2: EU large-cap pharma and the EMs

EMs account for nearly a quarter of global pharma sales

Given that the tropical disease activities of the pharma industry fall squarely within their Emerging Market (EM) businesses, we thought it may be useful for readers to recap on the scale of the companies' EM activities and their relative positioning. Taken as a whole, we believe Pharmaceutical sales in EMs reached $225bn (+8%) in 2013, equivalent to 23% of the global total (Figure 1). Within EMs, roughly 45% of sales derive from the so-called BRIC group of countries (Brazil, Russia, India, China) with the remaining 55% accounted for largely by around 50 small- to mid-sized countries. This same heterogeneous collection of markets accounts for around 85% of the world population, the massive mismatch between sales value and population indicating the theoretically significant upside potential for the pharma industry from EMs.

Figure 52: Global pharma market by sales (2013: $980bn, +2%)



Source: Deutsche Bank estimates, IMS Health)

Profitability in this diverse set of developing markets is inevitably below that of the West as a result of lower pricing. Nevertheless, the impressive volume growth opportunity - driven by improved healthcare infrastructure, a rising and increasingly affluent middle class and greater longevity (hence the increasing prevalence of chronic diseases such as hypertension and diabetes) - has been an important prop for the pharma industry during its 'patent cliff' and potentially represents a key source of long-term growth (the overall market leader Sanofi is especially bullish, describing EMs as "*the single biggest growth opportunity for the industry as a whole*").

In our '*Emerging markets for Beginners'* report (4 February 2011), we projected that EMs will generate around half of industry sales growth over the coming five years. IMS Health has tended to be more optimistic still, projecting that EMs will drive 60-70% of industry growth to 2017. Figure 53 shows IMS projections for the world's leading countries by pharma sales, as set out in its 2013 World review. By 2017 it expects six of the top 15 countries to be represented by EMs, with China set to overtake Japan as the world's #2 market and all four BRIC countries to feature in the top ten list.

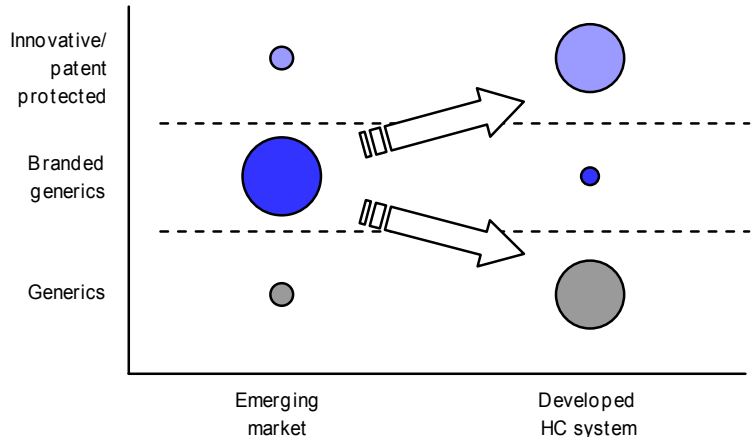
Figure 53: Top 15 pharma markets by sales

Rank	2007	2012	2017E
1	US	US	US
2	Japan	Japan	China
3	France	China	Japan
4	Germany	Germany	Brazil
5	China	France	Germany
6	Italy	Brazil	France
7	UK	Italy	Italy
8	Spain	Spain	Russia
9	Canada	Canada	India
10	Brazil	UK	Canada
11	Mexico	Russia	UK
12	South Korea	India	Spain
13	Turkey	Australia	Australia
14	Russia	South Korea	Argentina
15	India	Mexico	South Korea

Source: IMS Health Market Prognosis, World Review 2013

While we are relatively optimistic about the medium term growth opportunities (albeit not as bullish as IMS Health), we have consistently cautioned that we expect EMs ultimately to move towards the Western model, i.e. to bifurcate towards low-cost, local generics and novel premium-priced medicines (Figure 54). This will in the long run shift the emphasis away from branded generics (currently the largest part of EM sales) and towards innovation, especially for the non-domestic multinational companies.

Figure 54: Over time, innovation and generics look set to win out in EMs



Source: Deutsche Bank

European large-cap pharma generates 25% of sales in EMs

The larger European pharma companies are generally well represented in the EMs, generating 25% of sales from the region, representing a significantly higher average exposure than their US peers (see Annex 3). Individual company exposures inevitably vary, from AstraZeneca at the low end (21%) to Bayer (35%) and Sanofi (33%) at the high end (Figure 55), reflecting a combination of company history (including colonial pasts and the degree of focus on M&A in EMs), and the nature of product portfolios.

Figure 55: EU large-cap Pharma summary exposure to EMs (% sales, EBIT)

	EM as % Pharma*	EM as % Group	EM margin (est**)	EM as % group (core) EBIT
AstraZeneca	21%	21%	42%	27%
Bayer	35%	38%	14%	37%
GSK	24%	25%	28%	23%
Novartis	25%	25%	28%	28%
Novo Nordisk	23%	23%	34%	21%
Roche	24%	27%	35%	26%
Sanofi	33%	33%	36%	42%
Mean (ex-Bayer/Novo)	25%	26%	34%	30%

*Note: * 2013 FY figures; Pharma defined as branded and generic drugs plus vaccines (in case of Sanofi other businesses [CH, AH] included): Roche figures for International region; Novo for China plus International; GSK for EMAP; others for Emerging markets or Emerging growth markets;** pre-R&D margin; Bayer EM margin below peers due to MaterialScience and CropScience (Pharma EM margin assumed at c.30%)*
Source: Company data, Deutsche Bank

We estimate the profitability of the European companies' EM businesses is typically 20-50% below that in developed markets when looked at on a pre-R&D basis (where reported, companies generally do not apportion R&D spend to EMs, although we think this is increasingly questionable given our view on the long-term outlook for EMs, i.e. the increasing emphasis on novel, differentiated medicines, as opposed to branded generics). As shown in Figure 56, diversified market leader Sanofi has historically generated a pre-R&D margin in EMs of c.40% while GSK - with less critical mass - achieved a c.31% margin in 2013 (note: this was down from 33% in 2012 due to the collapse in its sales in China in 2H13).

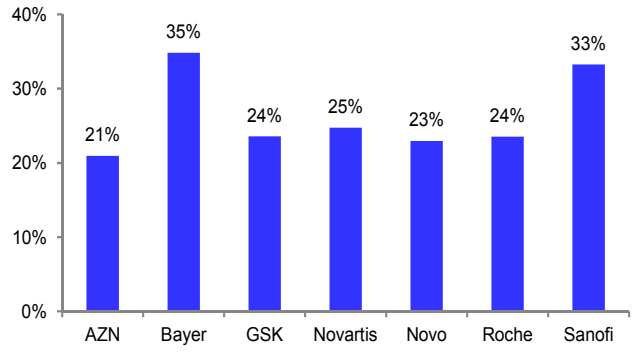
Figure 56: Profitability in EMs (where disclosed)

Company	EM profitability	Source
AstraZeneca	Pre-R&D operating margin (excluding central costs) was 76% of that in established markets in 2012, implying c.42%	Company general IR presentation, Feb 2013
GSK	2013 pre-R&D margin in EMAP region was 31% (as compared with 64% in established markets)	4Q/FY13 results press release
Sanofi	EM business operating margin forecast at "around 40%" excluding central administrative and R&D costs in 2011 (vs estimated pre-R&D margin for established markets of 49-50%)	IR "Strategy & Outlook" thematic seminar, Sep 2011

Source: Deutsche Bank, company data

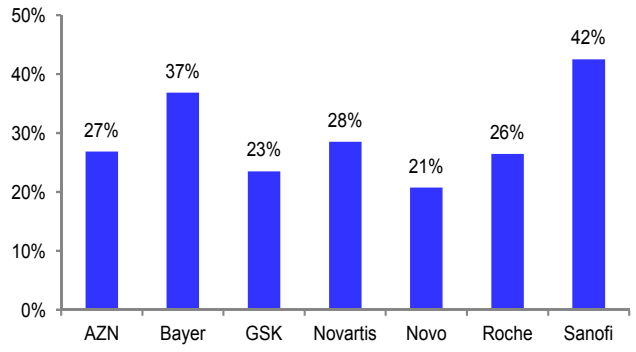
Excluding an allocation for R&D means that EMs nominally generate a similar proportion of group EBIT to their sales contribution, by our estimates. This is shown graphically in Figure 57 and Figure 58.

Figure 57: EMs as % Pharma/vaccines sales (2013)



Source: Deutsche Bank, company data

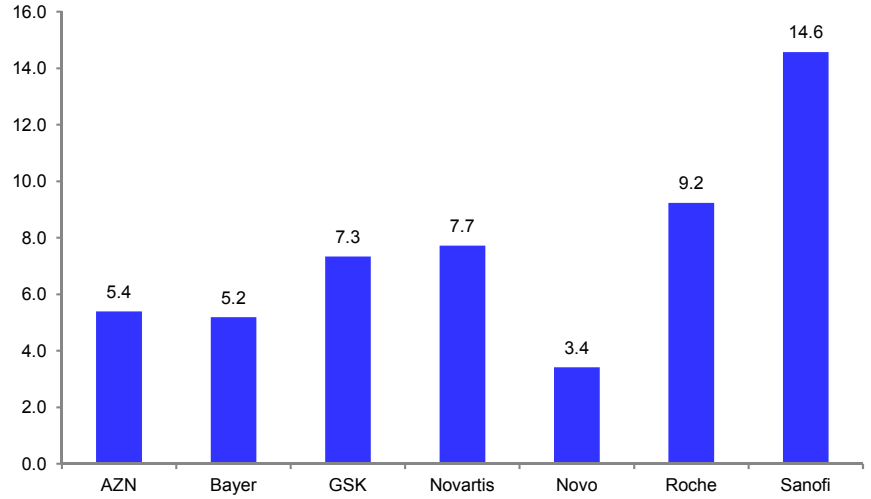
Figure 58: EMs as % group (core) EBIT (2013E)



Source: Deutsche Bank

Sanofi has materially higher level of EM sales versus peers

Figure 59: EM sales by EU large-cap Pharma (Pharma/vaccines; $bn; 2013)



Note: Roche slightly overstated as it reports International region sales, which include EMs and some developed markets
Source: Company data, Deutsche Bank estimates

Sanofi is the global leader in EMs (with a 5.7% share, according to IMS) and boasts strong positions in each of the main regions: it ranks #1 by sales in LatAm (including #1 in Brazil), #3 in China, #1 in Middle East & North Africa (MENA), #2 in CEE (Central & Eastern Europe), and #4 in Asia ex-China. Sanofi has in part built this position by a series of M&A deals, notably in Brazil (where it acquired Medley, the largest local generics company, for $660m in 2009), Mexico (generics player Kendrick acquired in 2009 for an undisclosed amount), CEE (Czech-based generic manufacturer Zentiva acquired for $2.6bn in 2008) and China (consumer health company BMP Sunstone acquired in 2010 for $521m). Buoyed by these deals, Sanofi's 2013 EM sales of €11.0bn ($14.5bn) were around double the average of its peers (Figure 59). Note that, in comparing sales levels, the definitions of EMs and disclosure levels vary (eg, AstraZeneca and GSK do not include CEE, bar Russia, in EMs while Roche's International region includes a mix of EMs and some developed markets).

Annex 3: Vaccines in EMs

A €7bn market growing at 11% pa

EMs currently account for close to a third (c.€7bn) of sales in the $25bn/€19bn global vaccines market. The emerging world, however, represents the vast majority of vaccine volumes: joint industry leader GSK has stated that just over 80% of the 860m vaccine doses it shipped in 2013 went to developing countries. In this case vaccines are generally purchased as part of bulk contracts by public organisations in support of mass vaccination programmes. Key public payers include governments and supranational purchasing organisations, notably UNICEF and PAHO (the Pan American Health Organisation). A major source of funding in the poorest nations is GAVI (Global Alliance for Vaccines & Immunisation), a public-private sector partnership that includes, amongst others, UNICEF/WHO, the World Bank, plus philanthropic individuals and organisations (eg, the Bill & Melinda Gates Foundation).

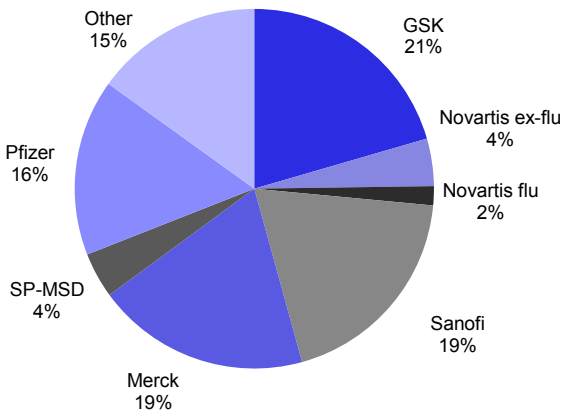
Projections cited by GSK and Sanofi suggest that global vaccine market growth will average at around 10% or 6-7% pa respectively in the coming years (Sanofi's forecast includes 4% growth in mature countries and 11% in the developing world). Double-digit growth in EMs is likely to be led by:

- Growing access to health provision, notably in larger EMs (eg, China).
- Improved funding in the poorer nations (through GAVI etc).
- Strong demand due to huge birth cohorts (there are c.124m births pa in the developing world, as compared with 4m in each of the US and W. Europe, including c.19m in China, 25m in India, and 4m in Brazil).
- Improving immunisation rates. For example, while Hib (a cause of bacterial meningitis) is all but eradicated in the West, only half of children in the EMs currently receive a vaccine to protect against this.
- New vaccines for tropical diseases. Notably GSK and Sanofi are developing innovative vaccines against malaria and dengue fever.

GSK and Sanofi lead the vaccines market, including in EMs

The global vaccine market is essentially an oligopoly with five manufacturers - GSK, Sanofi, Merck, Pfizer and Novartis - accounting for >80% of sales. GSK and Sanofi have historically led the market but Merck achieved a broadly similar market share in 2013 (through growth in its HPV and herpes zoster vaccines). GSK will, however, cement its position as overall industry leader in 2015 via the planned purchase of Novartis non-flu vaccine assets for $5.25bn cash plus up to a further $1.8bn (this will enhance its market share by 5% and add growing franchises in particular in meningitis B and C vaccines). With regard to the EMs specifically, GSK and Sanofi each vie for the number 1 position in vaccines in this heterogeneous group of developing countries. Together the two have a c.40% share of EM vaccines, we estimate.

Figure 60: : Global vaccine market (2013: $25bn/€19bn)



Note: SP-MSD (Sanofi Pasteur MSD) is a 50:50 European j/v between Merck and Sanofi
Source: GSK, Deutsche Bank

GSK is joint leader in EM vaccines and clear #1 in LatAm

GSK's vaccine sales in EMs reached £1,124m/$1,765m in 2013, accounting for close to a quarter of its global vaccine sales. Its EM region includes certain developed markets (Australia, New Zealand) but *excludes* Central & Eastern Europe (bar Russia) and thus is not strictly comparable with chief competitor Sanofi's definition of EMs. Nevertheless, by comparison, Sanofi's EM vaccine sales in 2013 were essentially identical at €1,341/$1,784bn.

Figure 61: GSK's EM vaccine sales by product, 2013 (£m)

Vaccine	Target	2013 sales	CER % change	% total
Synflorix	Pneumococcal infections	350	1	31
Rotarix	Rotavirus	164	3	15
Infanrix, Pediarix	DTPa + combinations (polio, HepB)	132	11	12
Hepatitis	Hepatitis A and B	123	-2	11
Cervarix	HPV	92	23	8
Fluaral, Flulaval	Influenza	43	-2	4
Boostrix	Adult booster	20	25	2
Other	Miscellaneous, incl. Priorix (MMR)	200	-14	18
Total		**1,124**	**1**	**100**

Source: Company data, Deutsche Bank

GSK and Sanofi each have a broad array of vaccines (Figure 62) covering most endemic and childhood diseases but the successful launches of the pneumococcal vaccine Synflorix (especially) and Rotarix have propelled GSK to its current leading position.

Figure 62: EM vaccine portfolios (d= development/registration)

	GSK	Sanofi	Merck	Novartis	Pfizer
DTPw combos	x	x		x	
DTPa combos	x	x			
MMR/Varicella	x	x	x		
Hepatitis A	x	x	x		
Rotavirus	x		x		
Meningococcal	x	x		x	
Pneumococcal	x				x
Influenza	x	x		x	
HPV	x		x		
Malaria	d				
Dengue		d			

Source: Company data, Deutsche Bank

GSK is especially strong in the vaccines market in Latin America, we believe, and comfortably leads the market ahead of Sanofi. While it does not supply sales figures by region, it revealed on an investor trip that we hosted in 2012 that its LatAm vaccine sales in 2011 were £422m, accounting for >40% of GSK's total EM vaccine sales (see our report *'LatAm investor field trip – key takeways'*, 28 March 2012). On the basis of additional figures supplied on that trip, we calculated that nearly three-quarters of GSK's Synflorix sales in EMs and around half of Rotarix and Cervarix sales in EMs are generated in LatAm.

Much of GSK's success in LatAm vaccines stems from a series of partnership deals with the Brazilian public health organization FioCruz. In particular, Synflorix became the company's top-selling product in LatAm in just three years, largely as a result of the technology transfer agreement struck in 2009 with FioCruz. Under this deal, GSK will supply $2.2bn of Synflorix to Brazil over a period of ten years, at the end of which the technology will be transferred to FioCruz. Prior to this agreement, GSK had operated a polio vaccine alliance (which lasted from 1985-2007) and a series of technology transfer deals, including vaccines for Hib (1998), MMR (2003), and rotavirus (ie, Rotarix; 2005). It also signed a deal in 2009 to jointly develop a dengue fever vaccine with FioCruz, although here it is many years behind Sanofi's Phase III vaccine candidate (it is not listed on GSK's website as being among its clinical-stage pipeline programs, thus we assume it is still in pre-clinical development).

Turning to other EMs, GSK is the leader in the supply of vaccines to the Asia-Pacific region and has been active in building capacity in China (a roughly $1bn market) through a series of local partnership deals. These include the formation of a flu vaccines joint venture with Shengzhen Neptunus (which GSK later bought out in June 2011) and a paediatric vaccines joint venture with Jiangsu Walvax (the second largest Chinese Hib vaccine manufacturer) which will initially supply the MMR vaccine Priorix. GSK's broad portfolio of vaccines in China includes, in addition to Priorix and Fluarix, vaccines for DTP (Infanrix), hepatitis (Havrix, Engerix B, Twinrix), varicella (Varilrix) and Hib (Hiberix).

GSK typically supplies the poorest EMs through bulk agreements with the supra-national purchasing organizations GAVI, UNICEF and PAHO. For example, it has struck agreements to supply 125m doses of Rotarix (at $2.50/dose) and 480m doses of Synflorix (worth $1.3bn over 10 years) through its GAVI Alliance, while the company operates bulk supply agreements on Rotarix, Synflorix and Cervarix with PAHO.

The key EM-targeted vaccine in GSK's pipeline, as detailed in this report, is the malaria vaccine RTS,S or Mosquirix. Although protection levels from the large Phase III trial in sub-Saharan Africa babies and infants have not met earlier hopes, further clinical data is awaited this year and the vaccine retains the potential to have a major impact on public health. As a non-profit venture it does not represent a meaningful commercial opportunity for GSK (we suggest in this report that it could potentially generate sales in the $80-130m pa range initially, buoyed by catch-up vaccination in the under-5 group, and the planned 5% return on sales will be reinvested in further R&D) but it may well have a profound benefit on the livelihood of millions in the developing world.

Sanofi ranks #2 in vaccines globally and joint #1 in EMs

Although its definition of Emerging Markets differs slightly from that of GSK, on the basis of its reported 2013 sales of €1,341m, Sanofi ranks joint #1 in EM vaccines (Figure 63). We estimate this equates to a market share of c.20%. The company's EM vaccine sales are concentrated in four main categories: multivalent paediatric vaccines (notably its Pentaxim 5-in-1 combination against DTP, polio and Hib); influenza vaccines (a category in which Sanofi is the global leader, with close to a 40% share by volume and value); travel & endemic vaccines; and meningitis vaccines.

Figure 63: Sanofi's EM vaccine sales by product, 2013 (€m)

Category	Key brands	2013 sales	CER change	% total
Polio/Pertussis/Hib	Pentacel, Pentaxim	644	34	48
Influenza	Fluzone, Vaxigrip	291	-6	22
Travel and other endemic	Miscellaneous	215	11	16
Meningitis/pneumonia	Menactra	132	-18	10
Adult booster	Adacel	48	11	4
Other vaccines	Miscellaneous	11	-33	1
Total		**1,341**	**11**	**100**

Source: Company data, Deutsche Bank

When Sanofi's and GSK's EM vaccine sales are compared product by product, the two portfolios reveal very different and generally non-overlapping strengths (Figure 64). Following its planned acquisition of Novartis' non-flu vaccine assets, GSK will compete more directly in the paediatric combination and meningococcal vaccine sectors, although it will still be the smaller player.

Figure 64: EM vaccine sales compared, Sanofi vs GSK (2013, €m)

	Sanofi	GSK
Paediatric combinations	644	156
Influenza	291	51
Pneumococcal		413
Meningococcal	132	
Rotavirus		194
Hepatitis	n.d.	145
HPV		109
Other (Travel & Endemic, Adult boosters)	274	260
Total	**1,341**	**1,326**

Note: shaded = leadership position; n.d. sales not specifically disclosed
Source: Company data, Deutsche Bank

GSK's success with Synflorix and Rotarix has seen it overtake Pfizer and Sanofi to attain the #1 position in LatAm. Nevertheless Sanofi maintains a strong position in the largely-public Brazilian vaccines market (it also holds a leading position in the tender-driven Mexican market, through Pentaxim and its local manufacturing and partnership with government-owned Birmex in flu vaccines). As for GSK, Sanofi's position in Brazil has been built mainly through relationships and agreements with health authorities and local vaccine companies. For example, the company announced a deal in January 2012 to supply inactivated polio virus (IPV) vaccine in conjunction with FioCruz. This follows the shipment of millions of doses of yellow fever vaccine to Brazil in 2008 in response to a yellow fever epidemic and the supply of 60m doses of H1N1 pandemic vaccine in 2010 in partnership with the Brazilian ministry of health. Sanofi also has a collaboration on flu vaccines with the Sao Paolo-based Butantan Institute. Growth in LatAm looks set to be driven by these public-private partnerships as well as the full rollout of newer vaccines (Menactra, Adacel) and, in the medium term, the launch of new products (notably the recently-approved hexavalent paediatric vaccine Hexaxim and the dengue vaccine, for which the company reported positive results from two pivotal Phase III trials, including a >20,000-patient LatAm study).

Elsewhere in EMs, Sanofi has a strong and growing position in China. Here the company and GSK are comfortably the two leading multinational vaccine suppliers (we do not have access to recent data but in 2008 the two companies each held a 10% share of the market, with local manufacturers holding 77% and other multinationals just 3%). Sanofi's position was initially built mainly on flu and Hib vaccines and has been expanded upon by the launches of Imovax polio vaccine (in 2009) and Pentaxim (May 2011). The latter was the first 5-in-1 paediatric combination vaccine to be made available in China. Future growth in China is expected to be supported by capacity expansion in flu vaccines (Sanofi is already the leading supplier of flu vaccines with a >20% market share) and launch of the rabies vaccine VRVg (rabies is a serious health problem in Asia with 40-60,000 dying pa and over 13m Chinese are thought to be eligible for post-bite prophylaxis, of which less than 1m receive human immunoglobulin, the current standard of care).

Sanofi's other key EM in vaccines is India. Here the company is the leading supplier of oral polio vaccine (OPV) and already held a >30% overall market share prior to the 2009 acquisition of local manufacturer Shantha (for up to €550m), which took its share to c.36% (three times that of nearest rival, GSK). In addition to its existing sales and manufacturing infrastructure, Shantha's key asset is the liquid pentavalent paediatric vaccine Shan5 (which contains whole cell pertussis, in addition to diphtheria, typhoid, Hib and HepB antigens). Although this encountered initial production difficulties, Sanofi recently (in May 2014) received prequalification (akin to regulatory approval) for Shan5 from the WHO. This allows the product to be considered for the second part of the 2013-15 UNICEF tender for pentavalent vaccines for the poorest nations (funded by GAVI). This tender amounts to around 200m doses pa at a current acquisition price of $2.50/dose, ie, annual sales of c.$500m (albeit prices are projected to fall with increased supply).

Looking ahead Sanofi has two very important EM-targeted vaccines in its portfolio, namely Hexaxim, the first fully liquid, paediatric vaccine to confer protection against six childhood and endemic diseases, and the innovative first-in-class dengue fever vaccine which is discussed in detail in this report:

- Hexaxim adds a hepatitis B component to the five diseases targeted by Pentaxim and is thus ideally suited to the needs of EMs. It was approved by the EMA in March 2013 under the Article 58 procedure (which allows the evaluation of medicines intended exclusively for markets outside the EU). Hexaxim could supplant Pentaxim as Sanofi's leading paediatric vaccine in EMs, in our view, and may allow it to capture share from other suppliers of pentavalent vaccines.
- As discussed, Sanofi's dengue fever vaccine recently reported positive data from the second large-scale Phase III trial. This supported the findings of the first pivotal trial with efficacy of c.60% and major public health benefits (reduced hospitalizations and severe dengue cases). As a consequence we expect the vaccine to be approved and widely adopted in endemic regions as well as for the military and travelers in such regions. Sanofi believes this could be a €1bn+ market opportunity which we think plausible given the scale of projected demand and the clear benefits from vaccination.
- Additionally, we note that Shantha is developing a rotavirus vaccine (which is planned to enter Phase III in 4Q14) and that Sanofi is testing two EM-targeted vaccines in Phase II: a TB vaccine (under license from SSI in Denmark) and a purified rabies vaccine (in a Vero cell line).

Annex 4: Glossary of institutions

Access to Medicine Foundation is a Netherlands-based international not-for-profit organisation dedicated to "addressing the challenges of access to medicine worldwide". It publishes the biennial Access to Medicine Index, the first Index to rank pharma companies with respect to their efforts to improve global access to medicine (most recently in 2012; next update is due in November 2014).

AMFm (the Affordable Medicines Facility – malaria) is an innovative financing mechanism, run by the Global Fund, designed to expand access to artemisinin-based combination therapies (ACTs) for malaria. Financial support comes from UNITAID, the UK Dept for International Development (DFID) and other donors. Under this, the Global Fund negotiates lower prices (up to 80%) with drug manufacturers and pays most of the reduced price as a co-payment, lowering the cost to first-line buyers of ACTs substantially. These buyers are expected to pass on much of the price benefit so that patients are able to buy ACTs across the public, private, not-for-profit and for-profit sectors at affordable prices.

ChEMBL-NTD is an open access database of primary screening and medicinal chemistry data directed at neglected diseases. It is operated by the European Bioinformatics Institute (EBI) at the Wellcome Trust Genome Campus.

DNDi (Drugs for Neglected Diseases initiative) is a collaborative, not-for-profit R&D organization which was formed in 2003 and seeks to deliver 11-13 new medicines by 2018 for neglected diseases including leishmaniasis, Human African Trypanosomiasis, Chagas disease, malaria, HIV and filarial diseases. Coordinated from Geneva, the DNDi collaborates with pharma companies, academia, public institutions and non-governmental organisations.

GAVI Alliance (Global Alliance for Vaccines and Immunisation) was formed in 2000 to fund vaccines for children in 73 of the world's poorest countries. It is a public-private partnership between the WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation, donor governments, international development and aid organisations, developing countries and the vaccine industry. It is key to the supply of pentavalent, pneumococcal and rotavirus vaccines and more recently rolled out campaigns for HPV, Japanese encephalitis and measles-rubella vaccines. It targets the immunisation of 243m children, saving 4m lives.

Global Fund (full name The Global Fund to Fight AIDS, Tuberculosis and Malaria) was created in 2002 to help finance the fight against the three pandemics of HIV/AIDS, TB and malaria. Based in Geneva, it disbursed close to $4bn in 2013 to help fund medicines, diagnostics, counselling, and prevention programs (eg, mosquito nets). It has been much the largest source of public funding for TB and malaria in recent years and an important source of funding for HIV. It is mainly funded by government donations but also attracts philanthropic and private sector funding (eg, Bill & Melinda Gates Foundation).

MMV (Medicines for Malaria Venture) is a not-for-profit public-private partnership, established in Geneva in 1999, which seeks "to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs". The MMV funds and manages R&D into new treatment and prevention options, supported by a network of public, private and philanthropic organizations (including GSK, Novartis, Sanofi and five other drug companies). Novartis' paediatric Coartem formulation was introduced in conjunction with the MMV.

MPP (the Medicines Patent Pool (MPP) was formed in 2010 to increase access to quality, affordable medicines for people living with HIV in developing countries. Funded through UNITAID, it facilitates voluntary licensing of key HIV drug patents and is endorsed by the WHO and the Group of 8 amongst others.

PAHO (Pan American Health Organization) is the world's oldest (founded in 1902) public health agency. It works to improve living standards and the health of those living in the Americas and serves as the regional office for the WHO.

PATH is a Seattle-based, non-profit organisation (founded in 1977) that focuses on a broad range of global health issues including maternal and child health as well as epidemic diseases in the developing world (eg, diarrheal disease, malaria and HIV). With a budget of over $300m it is one of the largest global health organisations. In 2011, it expanded its drug development program by affiliating with **OneWorld Health**, a US-based non-profit drug development organisation focused on drugs for the world's most vulnerable populations.

UNICEF (United Nations Children's Fund) is a UN program, based in New York, and is the world's leading organisation for improving the lives of children. It encompasses all aspects of the livelihood of children, including education, nutrition, human rights etc and in the context of this report is a vital agency in the promotion of childhood immunisation (including helping implement the Global Vaccine Action Plan which seeks to achieve 90% immunisation coverage of infants at the national level by 2020) and in the treatment and prevention of HIV/AIDS in children and adolescents.

UNITAID is a global health initiative, funded by a levy on airline tickets, which negotiates low prices on drugs, vaccines and diagnostics for HIV/AIDS, malaria and TB in developing countries. It works in conjunction with distribution organisations such as The Global Fund, MMV and Medecins Sans Frontieres

WHO (World Health Organisation) is the public health arm of the United Nations. Founded in 1948 and headquartered in Geneva, it is responsible for "providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends". It included 194 member states at the last count.

WIPO Re:Search (World Intellectual Property Organization) provides access (via a searchable, public database) to IP for pharmaceutical compounds, technologies, and know-how and data available for R&D for neglected tropical diseases, TB, and malaria. Founded in 2011, its members include a number of academic and medical institutions, tropical disease health agencies and organisations (including MMV and PATH) and pharma companies. Among the European pharma names, founder members include GSK, Novartis and Sanofi.

Annex 5: Valuation & Risks

AstraZeneca: Hold, PT 4,000p

We value AstraZeneca on a combination of PE (at parity to a sector target PE of 15x at 2015E EPS, reflecting the improved possibility of pipeline leverage post-2017) and DCF (WACC 8.5%; beta 0.9, ERP 5.5%, RFR from local 10-yr govt bond yields; TGR 2.5% (at the top end of the range we use for pharma, reflecting pipeline optionality)). The key upside and downside share price risks in our view relate to: the waxing/waning of M&A speculation involving Pfizer; business development activity; and pipeline news, notably in oncology.

Bayer: Buy, PT €125

Our price target is derived through an average of 2015E target PE (15x) and DCF. DCF utilizes WACC 8.5%, ERP 5.5%, Beta 0.9, TGR 2% - below LT GDP due to the cyclicality of MS and some product risks in pharmaceuticals, but in line with chemical and healthcare peers. Key risks include competition to Xarelto, late stage trial failures, and early generic entrants. Within CH anti-trust represents a threat to the recent proposed acquisition. In CS, soft commodity prices and weather patterns are critical, whereas performance of MS hinges on raw material prices and the global recovery.

GlaxoSmithKline: Hold, TP 1,500p

We value GSK based on an average of 2015E PE and DCF methodologies. We use a 10% discount to our targeted sector average 2015E PE of 15x, given greater uncertainty over GSK's growth outlook (China, Advair pricing dynamic and generics) and loss of 'blue sky' optionality arising from a number of relatively recent Phase III pipeline failures (MAGE-A3, darapladib, drisapersen) Our DCF utilises three stage cash-flow forecasts, a WACC of 8.5% (beta 0.9, ERP 5.5%, RFR based on local 10-yr govt bond yields) and TGR of 2%. Key risks relate to regulatory/pipeline news, execution of new drug launches, dilutive disposals, and the outcome of the SFO and China investigations.

Novartis: Hold; PT CHF83

Our target price is based on an average of 2015E target PE (sector target PE of 15x) and DCF (WACC of 8.5%: beta of 0.9, ERP of 5.5% and RFR based from LT government bond yields, terminal growth rate of 2%). Key positive risks include greater than expected cost savings, better than forecasted pipeline and higher than expected proceeds from divestments. Negative risks include disappointment from clinical trial data, particularly should LCZ696 or serelaxin fail to meet investor expectations or be rejected by the regulators. Other risks include FTC rejection of the proposed asset saps with GlaxoSmithKline, unexpected patent challenges and failure to execute on new drug launches.

Novo Nordisk: Hold, PT DKr240

Our price target is set by 2015E PE (sector target PE at 15x, Novo at a 30% premium due to its high growth stable business) and DCF (three stage cash-flow forecast, based on a WACC of 8.5% and terminal growth rate of 2.5%). Positive risks include milder than anticipated competition in diabetes and rapid adoption/approval of next-generation insulins analogues. Downside risks include tougher than anticipated competition particularly if biosimilar insulins create price competition for all market participants, and US pricing.

Roche: Buy, PT CHF295

Our target price is based on an average of 2015E target PE (15x) and DCF methodologies (WACC of 8.5%: beta of 0.9, ERP of 5.5%, RFR from LT government bond yields, and terminal growth rate of 2.5%). Key risks to Roche involve competition to its current franchise by disruptive technologies as well as eventual filing of biosimilar entrants to Herceptin, Rituxan and Avastin. Clinical risks include data readouts on immunotherapeutics (both internal and competitor drugs) as well as data from the MARIANNE study of Perjeta and Kadcyla.

Sanofi: Buy, PT Euro 92

Our TP is based on an average of 2015E PE (we apply a target sector multiple of 15x) and DCF (utilises three-stage cash flow forecasts, a WACC of 8.5%: beta 0.9, ERP 5.5%, RFR based on local 10-yr govt bond yields, and a TGR of 2%). Key risks relate to quarterly earnings delivery, competitor news in diabetes (notably uncertainty over the outlook for the US Lantus franchise relating to the timing and extent of biosimilar and branded competition), R&D news flow, volatility in EMs, and exchange rate movements.

Annex 6: Key references

Figure 65 below lists the key references and source material which we consulted in order to compile this report.

Figure 65: Sources and references for Deutsche Bank tropical diseases report

Accelerating work to overcome the global impact of neglected tropical diseases - a roadmap for implementation (WHO, 2012)
Sustaining the drive to overcome the global impact of neglected tropical diseases (WHO, 2013)
WHO website for factsheets on NTDs and other tropical diseases, plus updates on Ebola disease outbreak
World Malaria Report (WHO, 2013)
Access to Medicine Index, 2012
State of the Tropics 2014 report
Company responses to Deutsche Bank survey on tropical diseases
Company CSR websites and annual reports
Novartis' dedicated malaria website (www.malaria.novartis.com)
Medicines for Malaria Venture website (www.mmv.org)
Other NTD related websites (eg, www.wipo.int/research/en; sites.path.org/drugdevelopment)
Clinical trial information from www.clinicaltrials.gov
Miscellaneous medical journals (eg, Lancet, NEJM)

Source: Deutsche Bank

Appendix 1

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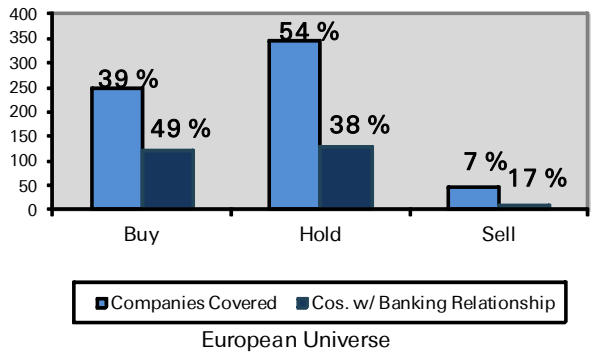

European Universe

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