Be Prepared! Global Pandemics Primer

Equity | Global | Thematic Investing
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Bank of America Merrill Lynch

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A Transforming World: Global Pandemics

As part of our work on A Transforming World, we introduce a new people-focused theme "Be Prepared!" with this pandemics Primer, setting out the challenges and opportunities presented by the theme of fighting pandemics.

We are living in the age of pandemics

As the current Ebola outbreak shows, the risk of a pandemic spreading globally is a question of "when" rather than "if". The danger looms large, with smallpox having killed 500mn in the 20th century, the 1918 Spanish Flu 30-100mn, and AIDS 30mn to date. The threat of a global pandemic is arguably higher than at any time in human history with risk factors including: globalisation, demographics, climate change, "zoonoses", unknown pathogens and re-emerging diseases, antimicrobial and antibacterial resistance, and laboratory escapes and bioterrorism. In this report, we outline the risk factors around 16 potential pandemics.

A severe pandemic could kill 360mn and hit global GDP by 5%

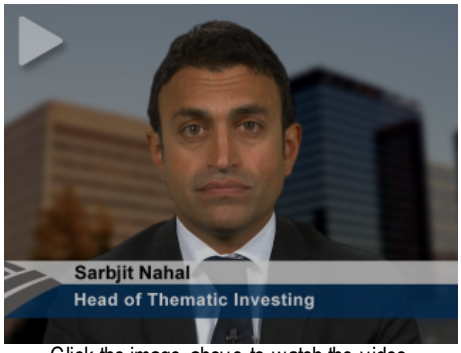
We estimate the potential costs of a pandemic to establish the price of its containment. Extrapolating historic examples, a severe and prolonged global pandemic could kill 180-360mn and hit global GDP by as much as 5-10% in the first year, with most industry sectors adversely affected, EMs hit the hardest, and the financial markets sliding into a major global recession off the back of widespread but highly unpredictable risk aversion. Worryingly, significant gaps exist in government funding for pandemic preparedness, and over three-quarters of corporates are thought to have inadequate pandemic plans.

Up to a US$2.5tn hit to the global economy

In terms of the potential sector impacts, a severe pandemic could hit demand for transport (air, road, rail, travel agencies), hotels and catering, restaurants, and arts and recreation by 67-80%. For many insurers, disease is the number one extreme mortality risk, and a severe pandemic could therefore wipe out 10-20% of the value from insured losses alone (not including financial market effects). The overall cost of a major global pandemic scenario including spillover across industry sectors could be as high as US$2.5tn (source: WTTC/Oxford Economics).

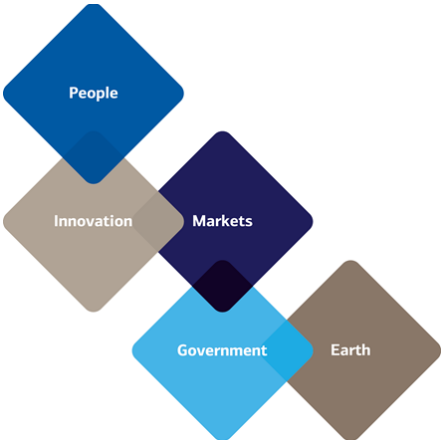
BofAML Global Fighting Pandemics stock list

We have mapped fighting pandemic exposure across a number of sectors' value chains to highlight a diverse range of entry points for investors wishing to play the pandemics theme: (1) Pharmaceuticals and Healthcare, (2) Life Sciences & Diagnostic Tools, and (3) Personal and Protective Equipment. Together with our sector analysts, we have created a list of close to 60 global stocks covered by BofAML that have exposure to pandemic-related solutions.



Click the image above to watch the video.

A Transforming World: Investment Themes



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Refer to important disclosures on page 94 to 96. Link to Definitions on page 93.

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The age of pandemics

The threat of a global pandemic is arguably higher than at any time in human history with risk factors including: globalisation, demographics, climate change, "zoonoses", unknown pathogens and re-emerging diseases, antimicrobial and antibacterial resistance, and laboratory escapes and bioterrorism.

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Extrapolating historic examples, a severe and prolonged global pandemic could kill 180-360mn and hit global GDP by as much as 5-10% in the first year, with most industry sectors adversely affected, EMs hit the hardest, and the financial markets sliding into a major global recession off the back of widespread but highly unpredictable risk aversion.

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Three entry points for investors

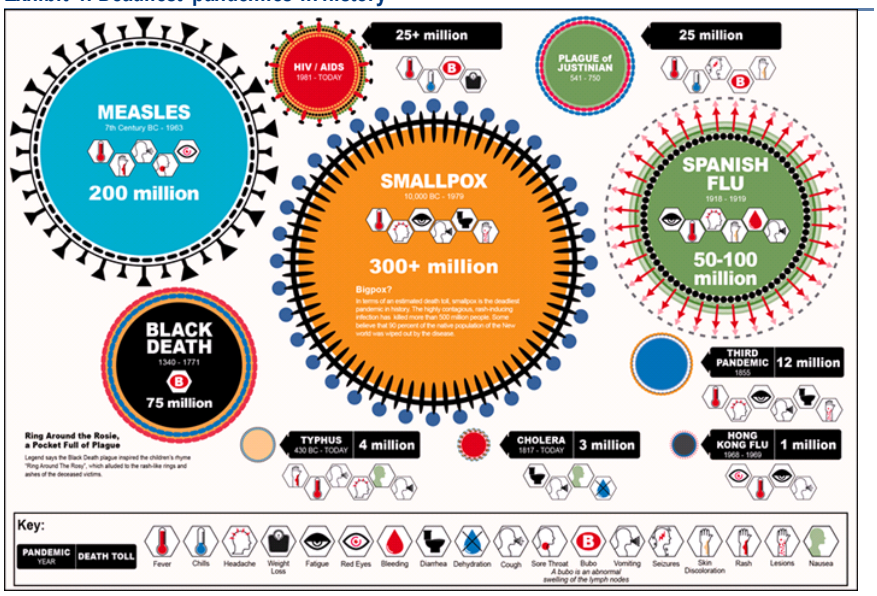
We highlight three entry points for investors wishing to play the fight against theme: (1) Pharmaceuticals and Healthcare; (2) Life Sciences & Diagnostic Tools; (3) Personal and Protective Equipment.

BofAML Global Fighting Pandemics stock list

BofAML Global Fighting Pandemics stock list is not a recommended list either individually or as a group of stocks

We believe that the global dynamics of the fight against pandemics mean that the theme offers numerous growth opportunities for those with exposure. Together with our sector analysts, we have created a list of over close to 60 global stocks covered by BofAML that have exposure to pandemic-related solutions.

Exhibit 1: Deadliest pandemics in history



Source: Good, Column Five, Mayo Clinic, CDC, WHO, NCBI, press sources, BofA Merrill Lynch Global Research

The BofAML Global Fighting Pandemics stock list of stocks is not a recommended list either individually or as a group of stocks. Investors should consider the fundamentals of the companies and their own individual circumstances / objectives before making any investment decisions

BofAML Global Fighting Pandemics stock list

We have created a BofA Merrill Lynch Global research list of stocks which have exposure to pandemic-related theme and that we consider could benefit long-term from the fight against global pandemics. The aim of the stock list is to provide investors with information to understand company and sub-sector opportunities and risks inherent in the pandemics theme.

Our Pandemics stock list

We have mapped a number of sector value chains to highlight 3 entry points for investors wishing to play the fight against pandemics theme:

1. Pharmaceuticals and Healthcare;
2. Life Sciences & Diagnostic Tools;
3. Personal and Protective Equipment

For each entry point, we highlight a diverse range of entry points for investors wishing to play the theme (i.e. exposure to products, technologies, services and solutions for the fight against pandemics).

Table 1: BofAML Global Fighting Pandemics Exposure Stocks

BBG Ticker	Company	Location	Market Cap (USD)	BofAML Ticker	Pandemics Sector	Exposure to pandemic-related solutions
Pharmaceuticals						
ABBV US	AbbVie	United States	92,729	ABBV	Pharmaceuticals	Antimalarials, TB/Hepatitis Treatment
ACT US	Actavis	United States	42,149	ACT	Pharmaceuticals	Antibiotic, Antiretroviral, Antifungal
APN SJ	Aspen	South Africa	13,633	APNHF	Pharmaceuticals	Antibacterials, Anti-fungal, Anti-retroviral
4503 JP	Astellas	Japan	33,054	ALPMF	Pharmaceuticals	Vaccines, Meningitis Treatment, Antiretroviral
AZN US	AstraZeneca	United Kingdom	90,764	AZN	Pharmaceuticals	MDR-TB, HIV Treatment
ARBP IN	Aurobindo Pharma	India	3,814	XLZFF	Pharmaceuticals	Antibiotics, Anti-retrovirals
BAYRY US	Bayer	Germany	118,086	BAYRY	Pharmaceuticals	Anti-infectives & Anitbacterials
BMY US	Bristol-Myers Squibb	United States	85,141	BMY	Pharmaceuticals	HIV/Hepatitis antivirals
CDH IN	Cadila Health	India	4,286	CDLHF	Pharmaceuticals	Vaccines
CIPLA IN	Cipla	India	7,898	XCLAF	Pharmaceuticals	HIV, TB, Malaria Treatment
CSL AU	CSL Ltd	Australia	33,296	CMXHF	Pharmaceuticals	Antiviral/Bacterial/Hepatitis, Diagnosis
1093 HK	CSPC Pharma	Hong Kong	5,236	CHJTF	Pharmaceuticals	Antibiotics
CBST US	Cubist	United States	5,648	CBST	Pharmaceuticals	Antibacterials
4568 JP	Daiichi Sankyo	Japan	12,011	DSKYF	Pharmaceuticals	Vaccines
DRTX US	Durata	United States	369	DRTX	Pharmaceuticals	Antibiotics
4901 JP	FUJIFILM	Japan	15,031	FUJIF	Pharmaceuticals	Potential Ebola treatment
GSK LN	GlaxoSmithKline	United Kingdom	112,200	GLAXF	Pharmaceuticals	Vaccines, Malaria/Ebola Vaccine, HIV
HIK LN	Hikma	United Kingdom	5,371	HKMPF	Pharmaceuticals	Antibacterials\virals, Anti-fungals, Anti-protozoal
IPXL US	Impax Labs	United States	1,707	IPXL	Pharmaceuticals	Antibiotics, Antivirals, Antibacterials
JNJ US	Johnson & Johnson	United States	305,713	JNJ	Pharmaceuticals	HIV, TB, Hepatitis Treatment
LPC IN	Lupin Limited	India	10,032	LPMCF	Pharmaceuticals	Global player in anti-TB
MRK US	Merck & Co.	United States	187,109	MRK	Pharmaceuticals	Vaccines
MYL US	Mylan Inc.	United States	18,523	MYL	Pharmaceuticals	TB therapeutics & HIV diagnosis
NOVN VX	Novartis	Switzerland	225,054	NVSEF	Pharmaceuticals	Antiviral, Antibacterial, TB/Malaria Treatment
PFE US	Pfizer Inc.	United States	225,615	PFE	Pharmaceuticals	Vaccines, Meningitis, Malaria, Smallpox, Polio, HIV
ROG VX	Roche	Switzerland	256,488	RHHBF	Pharmaceuticals	Hepatitis, HIV, TB Treatment
SAN FP	Sanofi	France	148,636	SNYNF	Pharmaceuticals	Vaccines
4555 JP	Sawai Pharma	Japan	2,079	SWPIF	Pharmaceuticals	Antibiotics
1177 HK	Sino Biopharma	China	5,037	SBMFF	Pharmaceuticals	Hepatitis Treatment
TEVA US	Teva	Israel	44,890	TEVA	Pharmaceuticals	HIV, TB, Hepatitis Treatment
MDCO US	The Medicines Co.	United States	1,480	MDCO	Pharmaceuticals	MRSA Treatment
TBPH US	Theravance	Cayman Islands	812	TBPH	Pharmaceuticals	Antibacterial, MRSA
ZTS US	Zoetis	United States	17,982	ZTS	Pharmaceuticals	Animal Vaccines

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Life Sciences & Diagnostic Tools						
ABAX US	ABAXIS	United States	1,186	ABAX	Life Sciences & Diagnostic Tools	Portable blood diagnosis
ABT US	Abbott Labs	United States	64,802	ABT	Life Sciences & Diagnostic Tools	Antivirals, HIV Diagnosis
BAX US	Baxter	United States	39,250	BAX	Life Sciences & Diagnostic Tools	IV's
BDX US	Becton Dickinson	United States	22,216	BDX	Life Sciences & Diagnostic Tools	Hypodermic needle/syringe leader
CAH US	Cardinal Health	United States	25,364	CAH	Life Sciences & Diagnostic Tools	Gloves, syringes & needles
CFN US	CareFusion	United States	9,624	CFN	Life Sciences & Diagnostic Tools	IV's, Sanitization
CTLT US	Catalent, Inc.	United States	2,812	CTLT	Life Sciences & Diagnostic Tools	Syringes, needles & medical supplies
CPHD US	Cepheid Inc	United States	3	CPHD	Life Sciences & Diagnostic Tools	MRSA, Meningitis diagnosis
CREM3 BZ	Cremer	Brazil	233	COQEF	Life Sciences & Diagnostic Tools	Surgical replace replaceiles
GRF SM	Grifols - A	Spain	14,107	GIFLF	Life Sciences & Diagnostic Tools	Diagnosis & Treatment
HSP US	Hospira	United States	8,864	HSP	Life Sciences & Diagnostic Tools	IV's, Medical delivery
ILMN US	Illumina	United States	24,929	ILMN	Life Sciences & Diagnostic Tools	Outbreak monitoring
LH US	Laboratory Corp	United States	8,661	LH	Life Sciences & Diagnostic Tools	Esoteric testing
MCK US	McKesson Corp.	United States	44,973	MCK	Life Sciences & Diagnostic Tools	Syringes, needles & medical supplies
MRK GR	Merck KGaA	Germany	40,731	MKGAF	Life Sciences & Diagnostic Tools	Diagnosis
QGEN US	Qiagen	Netherlands	5,699	QGEN	Life Sciences & Diagnostic Tools	Viral infection diagnosis, molecular flu test
SIE GR	Siemens	Germany	102,519	SMAWF	Life Sciences & Diagnostic Tools	HIV, Hepatitis, Malaria diagnosis
TMO US	Thermo Fisher	United States	48,879	TMO	Life Sciences & Diagnostic Tools	Instruments, Reagents, Flu Tests
WST US	West Pharma	United States	3,137	WST	Life Sciences & Diagnostic Tools	Drug delivery
Personal and Protective Equipment						
MMM US	3M	United States	93,046	MMM	Personal and Protective Equipment	Goggles, respirators, face masks & biohazard suits
ARG US	Airgas, Inc.	United States	8,444	ARG	Personal and Protective Equipment	Gloves, boots, biohazard waste bags, masks
ANN AU	Ansell	Australia	2,353	ANSLF	Personal and Protective Equipment	Healthcare barrier products
DD US	DuPont	United States	66,419	DD	Personal and Protective Equipment	Chemical protective clothing and biohazard suits
ECL US	Ecolab Inc	United States	35,790	ECL	Personal and Protective Equipment	Environmental sterilization
HON US	Honeywell	United States	74,282	HON	Personal and Protective Equipment	Spectacles, face shield, gloves and respirators
KMB US	Kimberly-Clark	United States	39,861	KMB	Personal and Protective Equipment	Gowns, drapes, gloves & masks

Source: BofA Merrill Lynch Global Research

The age of pandemics

"… a pandemic that kills 400 million people would eliminate world commerce; no planes would be in the sky for months, not to mention dealing with the rampant death and despair. It would totally change civilization, which makes it an existential risk." – Dr Larry Brilliant, ex-Skoll Global Threats Fund

We believe the 21st century is likely to see an increase in global pandemics – epidemics of infectious disease that spread through human populations across a large region, multiple continents, or even worldwide.

The threat of a major pandemic is a question of "when" not "if". We are seeing an increase in risk factors including: social (global mobility, population growth, urbanisation); economic (cross-border trade, globalisation of agriculture and food supply, illegal trade); environmental (climate change, changes in land use). We are witnessing an increase in the number of "zoonoses" – diseases that can spread from animals to humans – unknown pathogens and re-emerging diseases; pandemics becoming endemic; antimicrobial and antibacterial resistance; and the threat of laboratory escapes and bioterrorism. This combination of factors means that the risk of an epidemic of infectious disease spreading through human populations across large regions is arguably higher than at any time in human history.

Considerable doubts remain as to whether governments and corporates are sufficiently prepared for a major pandemic. While governments have made progress, with 158 having developed pandemic-preparedness plans (source: WHO), significant gaps exist with regard to funding, the availability of vaccines, R&D on dangerous pathogens and patent laws. Corporates are thought to be even less prepared, with over three quarters having inadequate pandemic preparedness plans, and one third thought to have no strategy at all (source: Marsh).

Pandemics 101

Definition

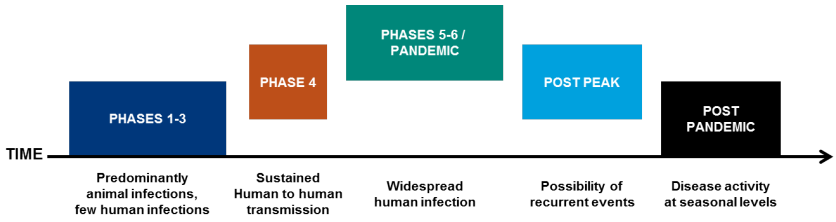
"An easy way to think about pandemic … is to say: a pandemic is a global outbreak. Then you might ask yourself: "What is a global outbreak"? Global outbreak means that we see both spread of the agent … and then we see disease activities in addition to the spread of the virus." - Dr Keiji Fukuda, WHO

A pandemic is an epidemic occurring on a scale that crosses international boundaries, usually affecting a large number of people. A disease or condition is not a pandemic merely because it is widespread or kills many people; it must also be infectious. For instance, cancer is responsible for many deaths but is not considered a pandemic because the disease is not infectious or contagious.

Six stages of a pandemic

The WHO has a six-stage risk classification that describes the process by which a novel influenza virus moves from the first few infections in humans through to a pandemic.

Chart 1: Pandemic phases



Source: WHO

The pandemic starts with the virus mostly infecting animals, with a few cases where animals infect people, then moves to the stage where the virus begins to spread directly between people, and ends with a pandemic when infections from the new virus have spread worldwide. Phases 1–3 correlate with preparedness,

including capacity development and response-planning activities, while Phases 4–6 clearly signal the need for response and mitigation efforts. Furthermore, periods after the first pandemic wave are elaborated to facilitate post-pandemic recovery activities (source: WHO).

Table 2: WHO pandemic alert protocol

Period	Phase	Characteristics
Inter pandemic	1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.
	2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.
Pandemic Alert	3	Human infections(s) with a new subtype, but no human-to-human spread, or at least rare instances of spread, to a close contact.
	4	Small cluster(s) with limited human-to-human transmission but spread is highly localised, suggesting that the virus is not well adapted to humans.
	5	Larger cluster(s) but human-to-human spread still localised, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible.
	6	Pandemic increased and sustained transmission in general population.

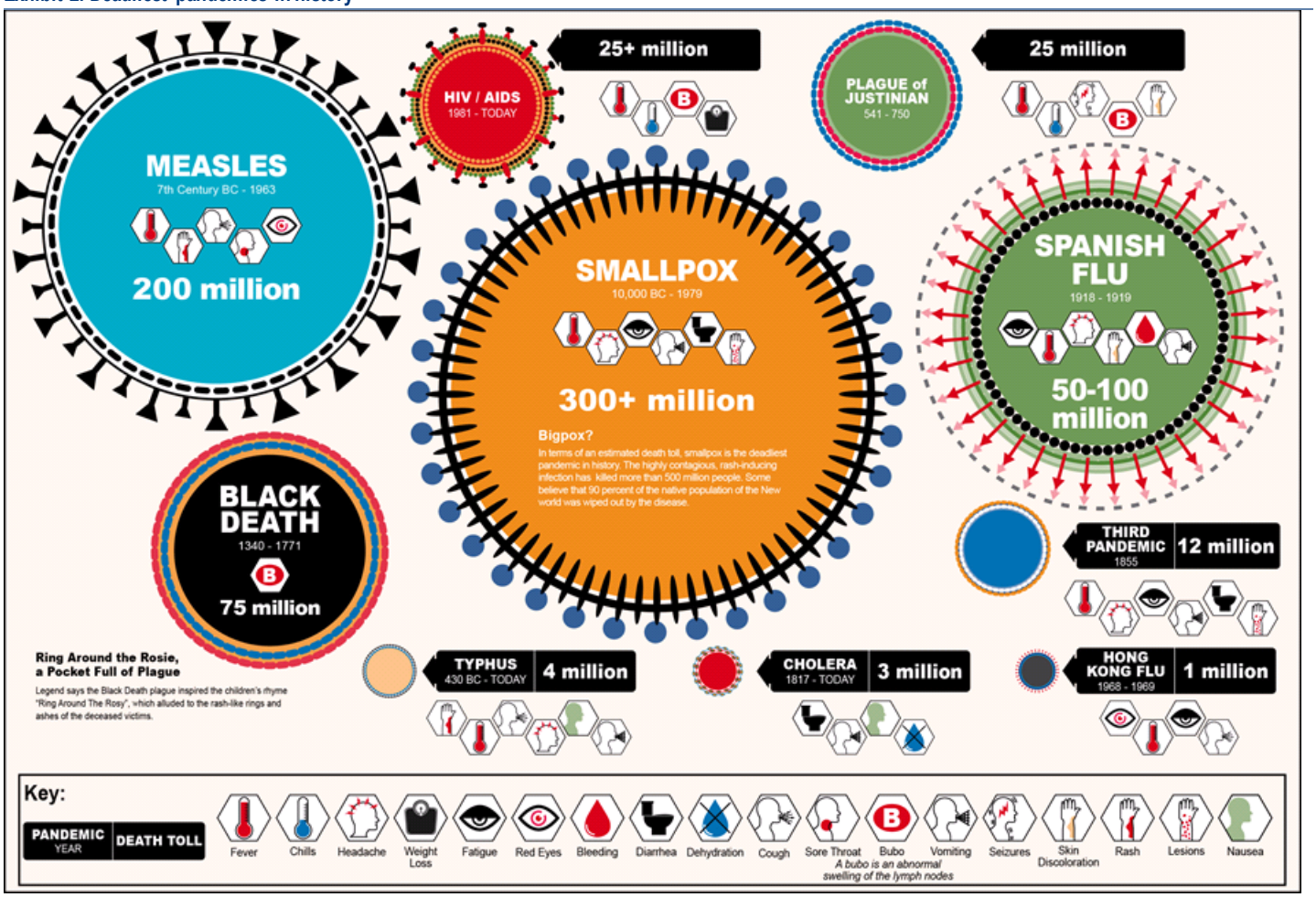
Source: WHO

Notable pandemics throughout history

A pandemic occurs approximately every 15-30Y. Thus, the annual probability of a pandemic is between 3% and 7% (source: Actuaries Institute)

There have been a number of significant pandemics recorded in human history, generally zoonoses, which came about with the domestication of animals, such as influenza and tuberculosis. Noteworthy historic pandemics include the Plague of Athens, Plague of Justinian, Black Death, and Spanish Flu. In this section, we outline a non-exhaustive list of 15 current or potential epidemics, and in the Appendix, we include a detailed list of historic pandemics with death counts.

Exhibit 2: Deadliest pandemics in history



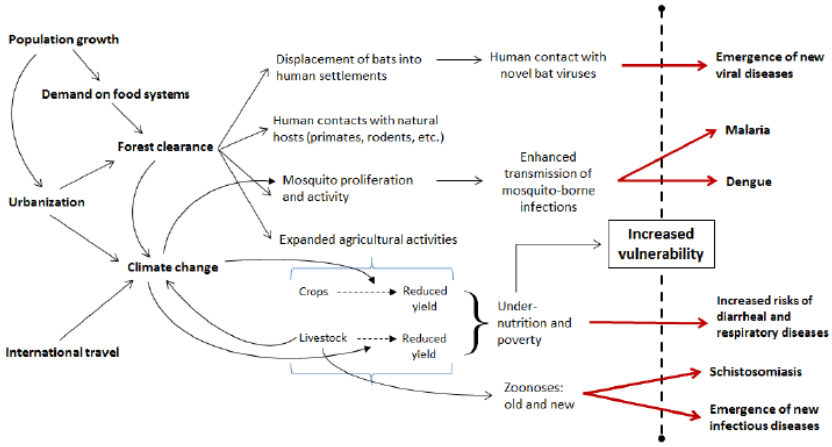
Source: Good, Column Five, Mayo Clinic, CDC, WHO, NCBI, press sources, BofA Merrill Lynch Global Research

"Why are more new viruses with pandemic potential jumping from their traditional animal hosts to humans now? If I had to choose a single word answer it would be: "modernity." If I had two more words, I would add "human irresponsibility." And of course so much of this peril is made much worse by the Great Exacerbator -- climate change and global warming". – Dr Larry Brilliant, ex-Skoll Global Threats Fund

Growing risk factors for pandemics

A combination of social, economic and environmental risk factors – as well as the threats of laboratory escapes and bioterrorism – means that the danger of an epidemic of infectious disease spread through human populations across large regions is arguably higher than at any time in human history.

Chart 2: Pandemic risk factors and their relationship to infectious disease emergence

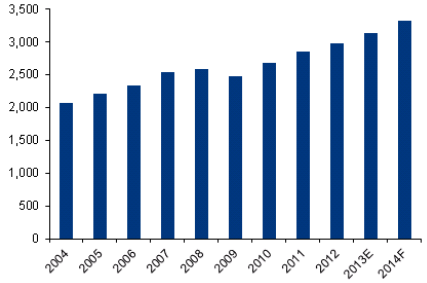


Source: McMaster Health Forum

Social risk factors

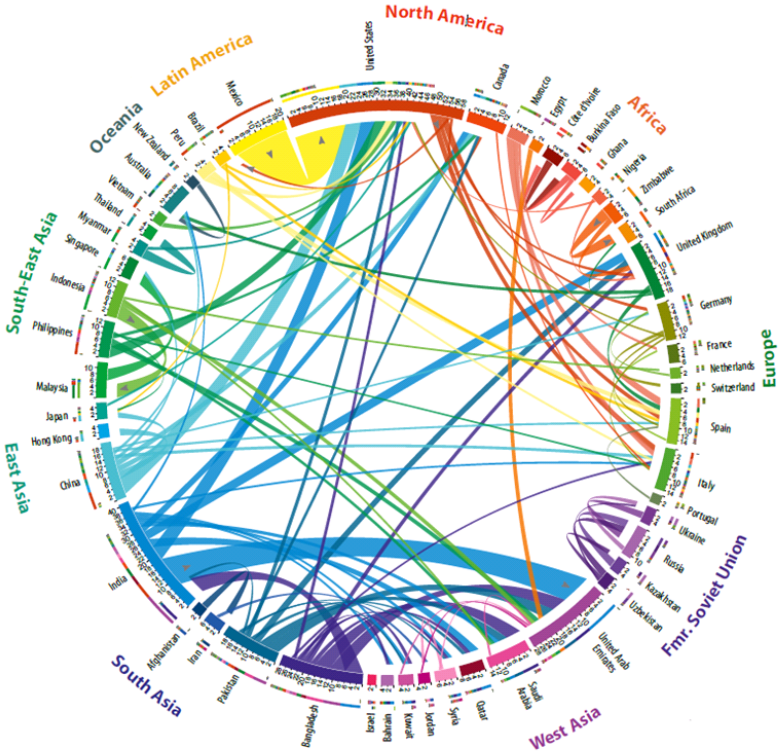
- **Increasing global mobility:** This means greater human exposure to risk factors and transmission of pathogens across borders. An estimated 3.1bn people used air transport in 2013 (+5% yoy) and the number of aircraft departures reached 33mn globally. By 2030E, the annual passenger figure is expected to reach 6.4bn (source: ICAO), with IATA estimating 16bn passengers and 400mn tonnes of cargo by 2050E.

Exhibit 3: Number of scheduled passengers in millions for global commercial airlines



Source: IATA

Exhibit 4: Global Migration Data Sheet 2005-10

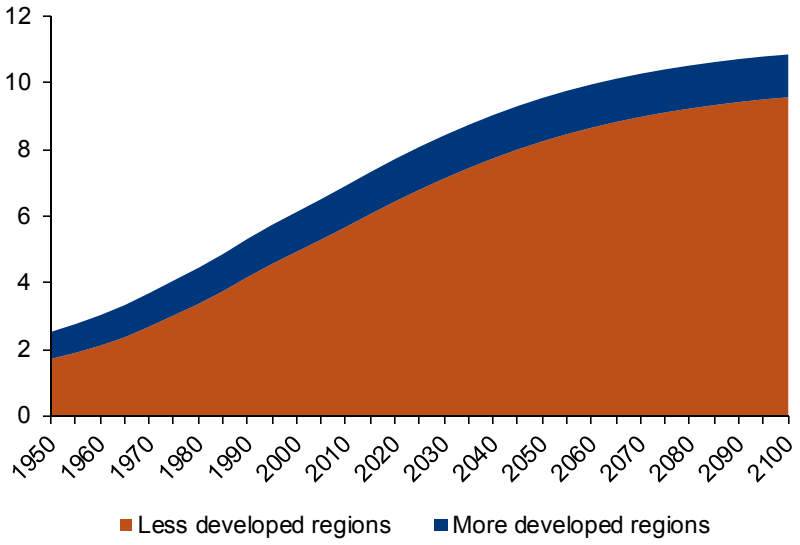


Source: Wittgenstein Centre for Demography and Global Human Capital

Global population will grow to 9-11bn by 2050, meaning growing pressure on food, water and energy

- **Population growth:** The UN estimates that the global population will grow to more than 9bn by 2050E, meaning increasing pressure on the food-water-energy nexus with demand for all three set to grow by 40-50% in the coming 20Y. Demographic changes have contributed to the emergence of a number of zoonoses, e.g. hantavirus pulmonary syndrome, monkeypox, SARS, and simian immunodeficiency virus (source: McMaster Health Forum).

Chart 3: Projected population growth by region

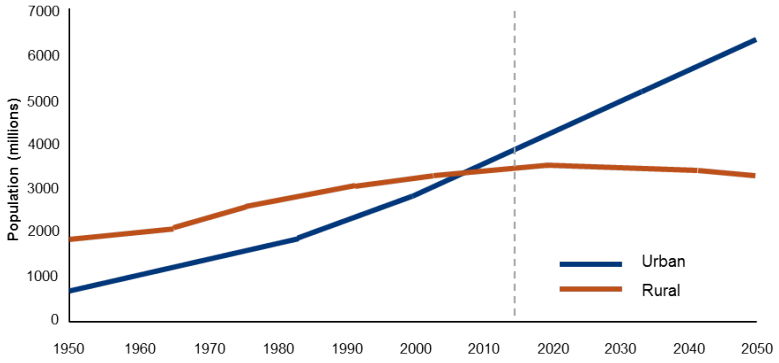


Source: UN

54% of the global population lives in urban areas and this will grow to 66% by 2050

- **Urbanisation:** 54% of the world's population lives in urban areas and virtually all countries are becoming urbanised. The UN estimates that the urban population will grow by 2.5bn by 2050E, or up to 66%. Increasing population density and person-to-person proximity could increase the risk of disease outbreaks and the rate of disease transmission, especially in rapidly urbanising EMs (source: Alicol et. al, Lancet Infectious Diseases 2011).

Chart 4: Global urban and rural population, 1950-2050



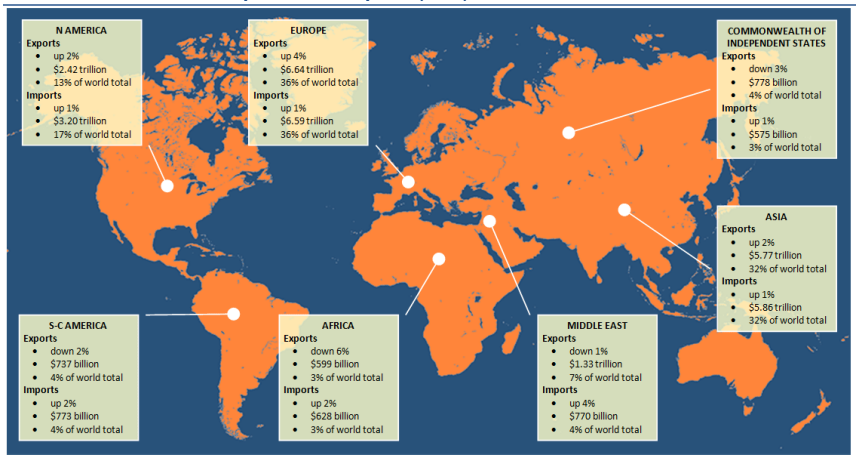
Source: UN World Urbanization Prospects 2014 Revision

Economic risk factors

World merchandise exports reached US$18.8tn and commercial services exports US$5.6tn in 2013

- **Increasing cross-border trade of goods, services and investments** is creating more opportunities for pathogenic agents (plant, animal and human) to spread. The WTO estimates that the dollar value of world merchandise exports reached US$18.8tn in 2013 (+2.1% yoy), while the value of commercial services exports reached US$5.6tn (+5.5% yoy).

Exhibit 5: Merchandise exports and imports (2012)



Source: WTO

Intensification of animal production (e.g. increasing prosperity and meat consumption – the number of chickens raised for food in China has increased 1,000x over the past few decades)

- **Globalisation of agriculture and food supply and systems** is facilitating the spread of zoonotic disease. The risk factor is likely to grow as animal production is intensified to achieve greater efficiency and economies of scale, which also provides more optimal incubating conditions for emerging zoonotic pathogens. The co-location of humans and animals in many EMs, along with increasing consumption of uncooked/undercooked meat provides additional opportunities for animal diseases to be transferred to human populations (source: McMaster Health Forum).

- **Illegal trade of animals, goods and people** encourages the spread of disease across borders and makes tracing such flows difficult (source: McMaster Health Forum).

Environmental risk factors

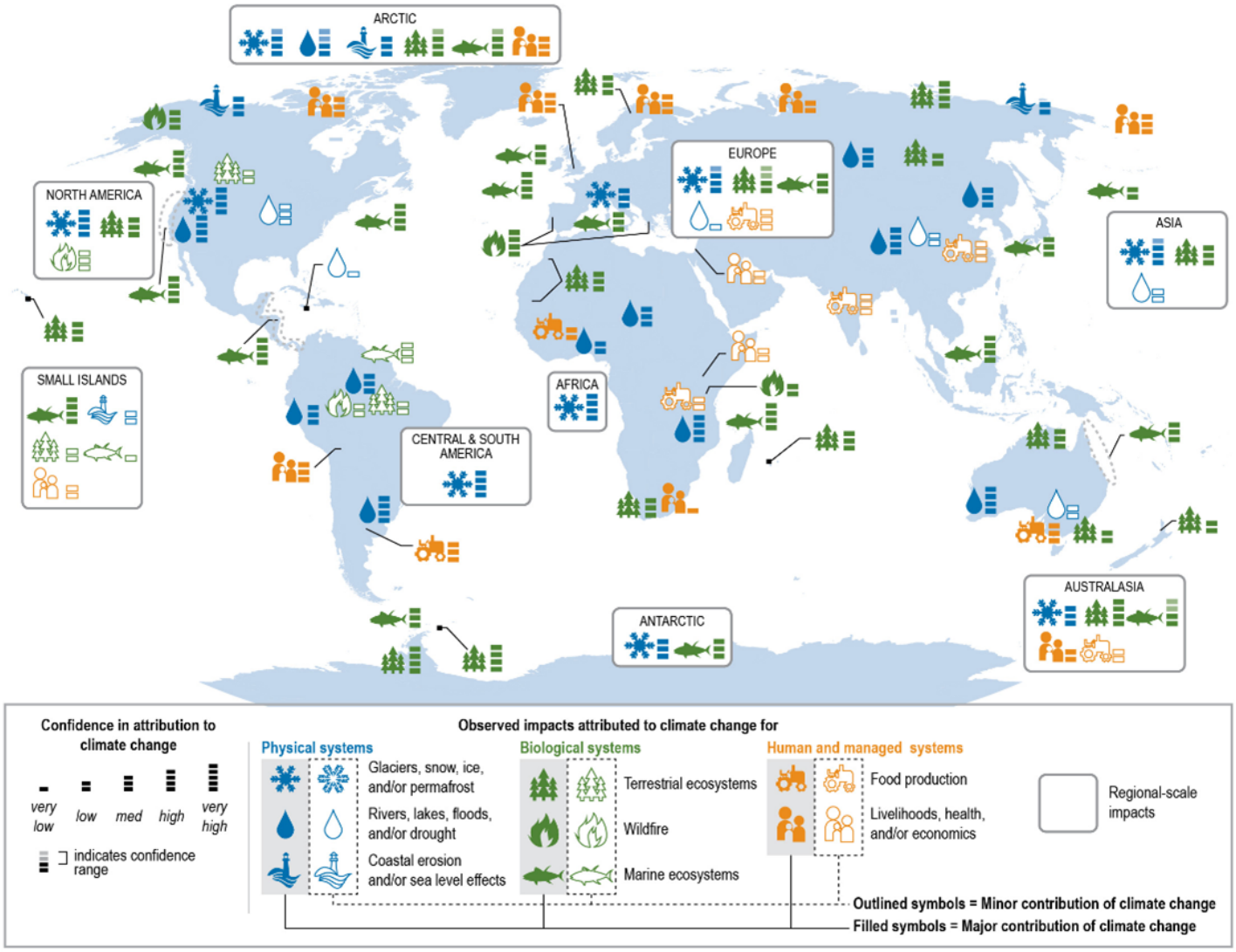
- **Climate change** is, according to a growing body of evidence, causing some vector-borne pathogens to proliferate beyond their traditional geographic range and seasonal time horizons off the back of variability and warming (e.g. malaria, cholera, dengue, Lyme disease, West Nile virus and tick-borne encephalitis).

Cutting down forests/jungles is eliminating the traditional barriers to zoonotic virus transmission to humans

Africans last year consumed c700mn wild animals or c2bn kg of "bush meat." (Larry Brilliant)

- **Changes in land use** off the back of growing resource demand/scarcity, extreme weather/climate change, deforestation/cutting down of the jungle, and changes in food production, mean greater human contact with animals and their viruses. It is also impacting food sources, water security, and waste management – with a knock-on effect on the way vector-borne pathogens are able to infect and be transmitted, and on how disease vectors are borne and propagated (e.g. affecting malaria, sleeping sickness, Chagas disease) (source: McMaster Health Forum).

Chart 5: How global climate change impacts various parts of the world



Source: IPCC, BofA Merrill Lynch Global Research

Pathogenic viruses that originate in animals and jump to humans – account for 60% of all infectious diseases, 75% of the annual 2.4bn emerging infections and 2.2bn deaths

Zoonotic diseases: 75% of emerging infections

Most of the focus on pandemic preparedness to date has centred on the real risk of the emergence of a pandemic influenza among humans. However, medical experts estimate that "zoonoses" – pathogenic viruses that originate in animals and jump to humans – account for 60% of all infectious diseases, 75% of the annual 2.4bn emerging infections and 2.2bn deaths (source: McMaster Health Forum).

Up to 1mn viruses could remain to be discovered

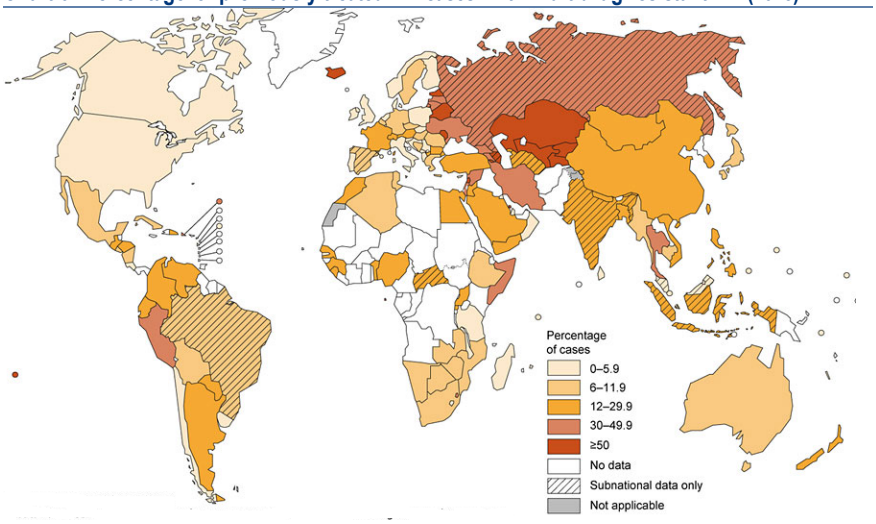
Some of these diseases are well-known: e.g. bird flu, SARS, HIV/AIDS, West Nile virus, monkeypox and Ebola. However, many are less known or remain to be found, with Columbia University's Ian Lipkin believing that there may be as many as 1mn viruses yet to be discovered. The combination of ubiquitous, naturally occurring diseases with pandemic potential and the social, economic and environmental factors described above, means that the risk of newly emerging zoonotic diseases and pandemics is only likely to grow.

If resistant gene mutations outpace antimicrobial innovations, decision-makers may have very limited options to contain pandemic spread

Growing antimicrobial and antibiotic resistance

The growing number of antibiotic-resistant microorganisms, sometimes referred to as "superbugs", threatens to undermine the ability of health systems to respond effectively to diseases that are currently well controlled. Recent examples include the spread of multidrug-resistant tuberculosis (TB) to tens of millions of people in c50 countries (source: WHO), and the emergence of methicillin-resistant *Staphylococcus aureus* as a community health threat in otherwise healthy individuals.

Chart 6: Percentage of previously treated TB cases with multidrug-resistant TB (2013)



Source: WHO

Frequent misuse of antimicrobials during non-pandemic and inter-pandemic periods diminishes their effectiveness and erodes their utility during a pandemic outbreak. Travel also increases the spread of antimicrobial and antiviral resistance (source: McMaster Health Forum). Coupled with the withdrawal of pharmaceutical companies from the antimicrobial market, this means that diseases that had been eradicated in certain regions are more likely to re-emerge.

"The question is not if such escapes will result in a major civilian outbreak, but rather what the pathogen will be and how such an escape may be contained, if indeed it can be contained at all."

High consequence breaches of biocontainment occur nearly daily: In 2010, 244 unintended releases of bioweapon candidate "select agents" were reported (source: Bulletin of Atomic Scientists)

Laboratory escapes: "self-fulfilling prophecies"

The risk of a manmade pandemic sparked by a laboratory escape is far from hypothetical, with many research labs manipulating already dangerous pathogens to monitor or tackle the natural emergence of pandemic strains. The Bulletin of Atomic Scientists highlights a number of instances of lab escapes of high-consequence pathogens resulting in transmission beyond lab personnel. The fact that many of these labs were working to prevent the outbreaks they caused leads the Bulletin to regard the consequences as "self-fulfilling prophecies".

Table 3: Details of laboratory escape-induced pandemics

Pandemic	Location	Escape	Impacts
H1N1 human influenza (1976-7)	China, US and USSR	Lab mishandling from facility trying to create a vaccine	Virus spread globally w/ an infection rate of 20-70% among those exposed; mild disease and a few fatalities
Smallpox (1963-78)	UK	3 escapes from 2 labs due to poor standards and bad practices	80+ deaths
Venezuelan equine encephalitis (1995)	Venezuela	Escape from lab	10,000 people in Venezuela and 75,000 people in Colombia fell ill, 311 deaths and 3,000 cases of neurological complications

Table 3: Details of laboratory escape-induced pandemics

Pandemic	Location	Escape	Impacts
SARS (2003-present)	China, Singapore and Taiwan	6 escapes from labs due to negligence and human error	No renewed outbreak
Foot and Mouth (2007)	UK	Virus escaped from biosafety lab	1,578 animals culled and cost £200mn

Source: Bulletin of Atomic Scientists

In 2003, Lord Martin Rees, ex-and President of the Royal Society, bet $1,000 that bioterror or bioerror would unleash a catastrophic event claiming 1mn lives in the next two decades

A dangerous game

Despite improvements in containment facilities and increasingly stringent biosecurity procedures for handling dangerous pathogens, inherent dangers remain: unrecognised technical flaws in standard bio containment; inadequately inactivated preparations of dangerous pathogens being handled in laboratory areas with reduced biosecurity levels; poor personnel training; slack oversight of laboratory procedures; and the fact that many university labs are in heavily populated urban areas (source: Bulletin of Atomic Scientists).

2014 CDC anthrax alert

In June 2014, 84 US Centers for Disease Control (CDC) scientists were exposed to a live strain of anthrax, with an investigation uncovering a number of safety lapses, including the use of expired disinfectant, the transportation of dangerous substances in Ziploc bags, and the storage of anthrax in unlocked refrigerators in unrestricted hallways.

Biological warfare and bioterrorism risk

The CDC has identified six "Category A" agents which pose a risk to national security, can be easily transmitted and disseminated, result in high mortality, have potential major public health impact, may cause public panic, or require special action for public health preparedness:

i) Tularemia or rabbit fever
ii) Anthrax
iii) Smallpox
iv) Botulinum toxin
v) Bubonic plague
vi) Viral hemorrhagic fevers

A biological warfare or bioterrorism-related attack involves the deliberate release of viruses, bacteria, toxins or other harmful agents to cause illness or death in people, animals, or plants (source: CDC). These agents are typically found in nature, but it is possible that they could be mutated or altered to increase their ability to cause disease or be spread into the environment, or make them resistant to current medicines. Biological agents can be spread through the air, water, or in food. Terrorists tend to use biological agents because they are extremely difficult to detect and do not cause illness for several hours to several days. Some bioterrorism agents, like the smallpox virus, can be spread from person to person and some, like anthrax, cannot.

Diseases considered or known to be used as a weapon include anthrax, Ebola, Marburg virus, plague, cholera, typhus, Rocky Mountain spotted fever, tularaemia, brucellosis, Q fever, Machupo, Coccidioides mycosis, Glanders, Melioidosis, Shigella, Psittacosis, Japanese B encephalitis, Rift Valley fever, yellow fever, and smallpox.

An attractive weapon but limited potential

Bioterrorism is an attractive weapon because biological agents are relatively easy and inexpensive to obtain, can be easily disseminated, and can cause widespread fear and panic beyond the actual physical damage. However, despite the media scrutiny, bioterrorism risk is limited by the difficulties of "effective" application against an "enemy". Technologists have warned of the potential power that genetic engineering could place in the hands of future bioterrorists.

Are we better prepared than for Spanish Flu?

The 1918 "Spanish Flu" infected 500mn people across the world including in remote Pacific islands and the Arctic, and killed 50-100mn, c3-5% of the world's population

A key factor in the impact of a pandemic is the strength of the pathogen itself: how easily it is spread, how infectious it is and the case mortality rate (source: Lloyd's). The next pandemic could thus be stronger or weaker than past examples such as the 1918 "Spanish Flu" global pandemic – an unusually deadly

influenza pandemic involving the H1N1 influenza virus. This infected 500mn people across the world including in remote Pacific islands and the Arctic, and killed 50-100mn, c3-5% of the world's population. Given that most scientists believe that the threat of an influenza pandemic is a "matter of when, not if" (source: WHO), we make some comparisons with 1918.

Arguments that we'd be better off than in 1918

- **Better drugs** including antivirals, vaccines for a second wave, fever reduction, and antibiotics.
- **A coordinated response** by the WHO managing a global response to the pandemic; the International Health Regulations placing legally binding responsibilities on nations; and the recent success story of the 2002-03 SARS.
- **Influenza models** have been developed by many stakeholders including within the insurance industry, to help better plan.
- **Better communication methods** notably ICT (television, radio, internet and social media) mean that the public can play an active role in combating the spread, and health professionals are better and earlier informed.
- **Healthier and better nourished populations** in many, but not all, cases (source: Lloyd's)

Arguments that we'd be worse off than in 1918

- **Global networks:** Many businesses are now part of a global network of suppliers and clients. Goods and materials including food are transported globally, potentially carrying pathogens. The "just in time" model of many businesses could lead to shortages of some drugs or even food.
- **Global travel:** In 1918, the pandemic spread quickly around the world due to demobilisation of troops following WW1. The number of people travelling round the world today using air, rail, motor and sea travel dwarfs 1918 levels and would likely quickly spread disease.
- **Larger population:** The global population is estimated at c7bn, nearly 3.5x its level in 1918. We can thus expect the numbers affected by a pandemic to be far greater, simply as a consequence of this larger pool of exposure, all other things being equal.
- **More concentration in cities:** For the first time in 2008, more people were living in cities than outside them vs 1918, when people were more dispersed due to more rural economies. Pandemics can spread quickly within cities due to denser populations and large number of commuters.
- **Large pools of sick people:** EMs have relatively large numbers of sick people, including those with AIDS (and hence immune deficiency), who will not be well equipped to fight a pandemic (source: Lloyd's).

Pandemic preparedness: we need to be doing much more

"The unavoidable reality is that tens of millions of people would be at risk of dying in a severe pandemic." - WHO

Considerable doubts remain about whether governments and corporates are sufficiently prepared to implement their plans in the case of a major pandemic. Recent pandemics such as H1N1 have shown a number of weaknesses,

including slow deployment of vaccines and poor communication, as well as the biggest gap – insufficient government spending on pandemic preparedness.

World has improved its capacity to respond

An estimated 158 countries had developed pandemic-preparedness plans, most of which were based on the anticipation of an outbreak of H5N1

The world has advanced its capacity to respond to global pandemics over the course of the past decade, notably to avian flu and SARS, As of 2011, an estimated 158 countries had developed pandemic-preparedness plans, most of which were based on the anticipation of an outbreak of H5N1 (source: WHO). Some governments have also stepped up their spending on vaccines and antiviral drugs. Other advances include better research into viruses, rapid amplification of DNA segments, and genomic sequencing advances.

But governments have a long way to go

Improved pandemic response planning needs to encompass a variety of factors:

- **Better global pandemic governance**, including enhancing national health systems' ability to detect pandemic risk factors, identify the causal pathogen, characterise the emerging disease and monitor its evolution.
- **Better availability of vaccines**, including public-private partnerships and contracts (e.g. the US's Biomedical Advanced Research and Development Authority work with pharma companies such as GSK and Novartis), guaranteeing governments a share of vaccines, and donating a percentage of vaccines to EMs.
- **Better R&D on dangerous pathogens** despite the inherent safety and security issues (i.e. bioterrorism, lab accidents).
- **Reform of patent laws** so that therapies exploiting the discovery of specific genes can be patented (as opposed to DNA itself).

US discovers it is ill prepared

A majority of the DHS's antiviral drugs are due to expire next year, that most of its hand sanitiser stock has already expired, and that its agencies do not know where to find their PPE

A telling and worrying sign of how governments are unprepared for a pandemic is the August 2014 US Department of Homeland Security (DHS) inspector general's report saying the majority of the DHS's antiviral drugs are due to expire next year, that most of its hand sanitiser stock has already expired, and that its agencies do not know where to find their personal protective equipment (PPE).

- 81% of the department's antiviral drugs are due to expire by 2015;
- 84% of its hand sanitiser stockpiles have expired, some by up to four years; and
- a lack of proper inventory controls, supply-replenishment plans and compliance with department guidelines (source: US DHS).

Table 4: US DHS recommendations for better pandemic preparedness

Rank	Recommendation
1	Identify and designate an office responsible for the management and accountability of pandemic PPE. We recommend the office designated for the management and accountability of pandemic PPE.
2	Develop a strategy for management, storage and distribution of pandemic PPE.
3	Implement an inventory system for the current inventory and future inventories of pandemic PPE.
4	Work with components to establish a methodology for determining sufficient types and quantities of pandemic PPE to align with the department-wide pandemic plan.
5	Have components implement inventory control procedures for pre-positioned pandemic PPE to monitor stockpiles, track shipments and ensure compliance with departmental guidance. We recommend the DHS MCM Working Group and OHSA.
6	Determine requirements of antiviral MCM for the Department to maintain critical operations during a pandemic. We recommend OHA.
7	Create an antiviral MCM Acquisition Management Plan to include: a) a methodology for determining the ideal quantity of antiviral MCM OHA will stockpile and how frequently it will be evaluated; b) a replenishment plan; and c) inventory tracking, reporting and reconciliation procedures for existing stockpile and new antiviral purchases.
8	Revise procedures to ensure proper contract oversight by government employees for management of its MCM support service contracts and ensure the contracting officer's representatives follow procedures:
9	Finalise and issue antiviral MCM guidance on the storage conditions, security and distribution for the antiviral MCM for all components.
10	Finalise the antiviral MCM recall it has initiated on the CBP, ICE, FEMA and USSS inventories.
11	Collaborate with CBP to determine the safety and effectiveness of the antibiotic MCM that have been stored alongside their antivirals.

Source: Office of Inspector General - Department of Homeland Security

More than three-quarters of companies are not prepared

Over three-quarters of companies have inadequate plans for coping with a flu pandemic

Pandemics are not "normal" business continuity risks – they are typically far more sudden, have a universal, disruptive impact on business and the economy, and impact larger numbers of people. During a potential pandemic, the ability of a company to respond quickly and effectively will make a huge difference to the success of protecting staff, profits and reputation (source: Marsh). However, research from Marsh suggests that over three-quarters of companies have inadequate pandemic preparedness plans, with one-third thought to have no strategy at all:

- Over three-quarters of companies have inadequate plans for coping with a flu pandemic.
- Around a third of businesses have no strategy at all, while 14% have only rudimentary contingency plans.
- Around a third of executives are unaware of how their companies intend to deal with the threat, with only 22% are comfortable that they are prepared (source: Marsh).

Critical pandemic questions for companies

Marsh sets out a number of issues companies need to consider when planning for pandemic preparedness:

- Consider the features of a pandemic disease and why it is different from a conventional business continuity risk.
- Consider the impact of an outbreak on your organisation and how you might recover – many existing business recovery plans are not well suited to situations where a proportion of the workforce is lost or there is a major disruption of the national and/or global environment.

- Review existing risk management and BCM plans and amend them based on an interpretation of the renewed threat.
- Set up an Emergency Response Team.
- Set up a Business Recovery Team that can cope with the specific problems triggered by an outbreak (source: Marsh).

Up to 360mn deaths % 5 hit on GDP

"For a severe pandemic we have seen that a global recession would be a likely result; so many businesses will be struggling, food may be short in some areas if supply chains are affected. Society will not be operating as it ordinarily does. We saw in the aftermath of hurricane Katrina the breakdown of law and order, and the looting that followed. This was at a time when the majority of the US was not affected; in a pandemic it is possible that the entire planet will be suffering the effects simultaneously or in quick succession" (source: Lloyd's)

Estimating the potential economic impact of a pandemic carries a high degree of uncertainty given that we have not experienced a major global pandemic in recent times: we do not know if, when and where it will; happen; and it is difficult to extrapolate predictions about behaviour from previous pandemics, such as Spanish Flu, in light of the advances in medical technology and globalisation.

However, we attempt to estimate the potential costs of a pandemic to better establish the cost of its containment. In this section, we explore the macro impact on economic activity of a severe and prolonged pandemic, which could be as high as 5-10% of GDP in the first year, with most industry sectors being hit negatively and EMs the hardest, and the financial markets sliding into recession off the back of widespread and largely unpredictable risk aversion.

Table 5: Estimated GDP losses by region from a future pandemic (% of GDP)

Country/ Region	Author	Range of estimates (min to max)
EU-25	EC - Directorate-General for Economic and Financial Affairs (2006)	1.6 – 4.1
USA	Congressional Budget Office (2005)	1.5 -5.0
Canada	James and Sargent (2006)	0.2 – 1.0
Germany	FT Deutschland 17/1. 2006	1.1 – 3.3
World	McKibbin and Sidorenko (2006)	0.8 – 12.6

Source: European Commission 2006

Infection rate & mortalities

Historically, infection rates have risen to as high as 25-35% of the population

Two key medical variables related to the pandemic are crucial for the estimation of potential mortalities: the morbidity rate (the percentage of the population infected), and the mortality rate (the percentage of those infected that die).

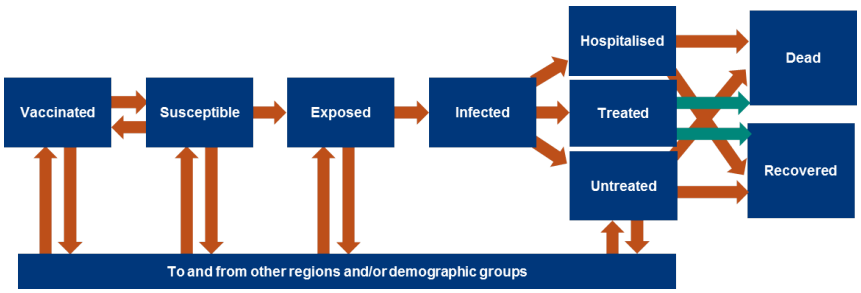
2-360mn deaths

If 1918-19 mortality data are extrapolated to the US population, 1.7mn people could die, half of them between the ages of 18 and 40. Globally, those same estimates yield 180-360mn deaths (source: Osterholm)

Historically speaking, infection rates have risen to as high as 25-35% of the population (source: WHO), spreading globally in as little as 180 days (source: RTI). In terms of potential mortalities:

- **A normal flu season kills some 0.2–1.5mn** (source: WHO);
- **A mild new virus could result in 2mn to 7.4mn deaths** (e.g., extrapolating from the 1957 Asian Flu pandemic) (source: WHO);
- **A more virulent virus could kill as many as 1 in 40 infected individuals** (source: Barry 2005) or some 71mn, with some experts suggesting that as many as 180-360mn could die in a worst-case scenario (source: Osterholm 2005) (e.g., extrapolating from the 1918 Spanish Flu pandemic).

Chart 7: Modelling the infectiousness and virulence of pandemics



Source: Vertikios et al., The Global Economic Effects of Pandemic Influenza, 14th Annual Conference on Global economic Analysis (2011)

Severe pandemic: 5-10% hit to GDP in first year

A mild pandemic would reduce output by less than 1% of GDP, a moderate outbreak by over 2%, and a severe pandemic by almost 5%, constituting a major global recession

There is little consensus on the economic impact of pandemics with results varying widely, according to the models used and availability of data. Any estimate of a pandemic's potential effects must combine two sets of assumptions:

- Spread and impact of pandemic from a medical/health perspective (morbidity rate, number of work days/weeks lost, mortality rate); and
- Choice of economic model and techniques to estimate the economic effects.

The World Bank's estimates – which are broadly in line with those of experts in the field including insurers such as Lloyd's – are that for the world as a whole. A mild pandemic would reduce output by less than 1% of GDP, a moderate outbreak by over 2%, and a severe pandemic by almost 5%, constituting a major global recession. Generally speaking, EMs would be hardest hit – with up to a 10% contraction in GDP – because higher population densities and poverty accentuate the economic impacts in some countries (source: World Bank).

Table 6: Possible economic impacts of flu pandemic

(% change in GDP, first-year)	Mild	Moderate	Severe
World	**-0.7**	**-2.0**	**-4.8**
High-income	-0.7	-2.0	-4.7
Developing	-0.6	-2.1	-5.3
East Asia	-0.8	-3.5	8.7
Europe and Central Asia	-2.1	-4.8	-9.9
Middle-East and North Africa	-0.7	-2.8	-7.0
South Asia	-0.6	-2.1	-4.9
Deaths (millions)	**1.4**	**14.2**	**71.1**

Source: World Bank calculations based on McKibbin & Sidorenko. Scenarios: mild = modelled on the 1968-69 Hong Kong flu; moderate = modelled on 1957 Asian flu; and severe = modelled on 1918-19 Spanish flu

Possible impacts of a Spanish flu-like pandemic

The largest impact is actually from changes to behaviour to avoid infection

Modelling a potential pandemic based on the Spanish Flu of 1918 helps to understand some of the factors driving the aggregate numbers in such simulations. The total impact of a shock combining all these elements is 3.1% for the global economy and ranges from 4.4% in Latin America and the Caribbean to 2.6% in the East Asia and Pacific region, mainly reflecting the relative importance and labour intensity of tourism and other services in each region. The impact on aggregate production from an infection rate of 35% of the population is over 2x larger than from loss of life itself. The largest impact is actually from changes to behaviour to avoid infection (e.g., reducing air travel, avoiding travel to uninfected destinations, reducing consumption of services such as restaurant dining, tourism, mass transport, non-essential shopping) (source: World Bank).

Table 7: Breakdown of economic impact of a potential Spanish Flu-like human-to-human pandemic (% of GDP)

	Mortality	Illness and Absenteeism	Efforts to avoid infection	Total	Total (USD bn)
		(% of GDP)			
World total	-0.4	-0.9	-1.9	-3.1	-1,526
High income countries	-0.3	-0.9	-1.8	-3.0	-1,131
Low and middle income countries	-0.6	-0.9	-2.1	-3.6	-405
East Asia and Pacific	-0.7	-0.7	-1.2	-2.6	-99
Europe and Central Asia	-0.4	-0.7	-2.3	-3.4	-83
Latin America and the Caribbean	-0.5	-0.9	-2.9	-4.4	-118
Middle East and North Africa	-0.7	-1.2	-1.8	-3.7	-25
South Asia	-0.6	-0.8	-2.2	-3.6	-37
Sub Saharan Africa	-0.6	-0.9	-2.2	-3.7	-26

Source: World Bank. Assumptions: a) globally 1.08% of the world population dies; b) for every person that dies, 3 are seriously ill; c) modelled as a demand shock (i.e. 20% decline in travel, restaurants, hotels, tourism, theatres); d) total impact in 2006$

US pandemic scenario analysis: up to 4.25% GDP hit

US CBO's severe pandemic scenario: gross attack rate of 30%, 2mn are assumed to die, real GDP would be 4.25% lower yoy than it would have been if the outbreak had not taken place

At the request of the US Senate, in 2006, the Congressional Budget Office prepared an assessment of the possible macroeconomic effects of an avian flu epidemic. The CBO report presents a severe and a mild scenario[1]:

- **Severe scenario**: 90mn Americans are infected – corresponding to morbidity or gross attack rate of 30% – and of these about 2mn are assumed to die, corresponding to a mortality rate (case fatality rate) of 2.5%. In this scenario, which is akin to the 1918-19 Spanish Flu pandemic, the CBO estimates that real GDP would be 4.25% lower yoy than it would have been if the outbreak had not taken place. That estimate is comparable to the effect of a post-World War II business-cycle recession.

- **Mild scenario**: the attack rate is set at 25% (c.75mn) and the fatality rate at 1.14% (c.100,000). In this scenario, which resembles the 1957 and 1968 pandemics, real GDP would decline by 1% relative to it having not taken place. The CBO believes this would probably not cause a recession and might not be distinguishable from normal variations in economic activity (source: CBO).

Up to an 80% decline in demand in a severe scenario for some industries

Industries that require interpersonal contact are assumed to have the largest declines in demand (e.g., entertainment, arts, recreation, lodging, and restaurants)

To calculate demand-side effects, the CBO examined GDP by industry and assumed different declines in demand for different industries, based on judgments about the degree of social interaction required in different industries. Industries that require interpersonal contact are assumed to have the largest declines in demand (e.g., entertainment, arts, recreation, lodging, and restaurants). Other industries were assumed to suffer a smaller decline in demand (e.g., retail trade, wholesale trade, and manufacturing). In contrast, there would be a surge in demand for medical care, which the CBO assumed would rise 15% relative to a base case without a pandemic. For the mild scenario, the CBO assumed that the demand-side declines in each industry were one-quarter of the decreases in the severe scenario.

[1] A number of additional assumptions are made concerning weeks off work across various sectors, etc. These numbers are derived from studies of past pandemics. It is important to stress that the perspective is a domestic U.S. one and the worldwide consequences are not considered, nor are the trade effects on the U.S. economy.

Table 8: US assumed declines in demand by industry in event of an avian flu pandemic (%)

	Severe Scenario	Mild Scenario
Private Industries		
Agriculture	10%	3%
Mining	10%	3%
Utilities	0%	0%
Construction	10%	3%
Manufacturing	10%	3%
Wholesale trade	10%	3%
Retail trade	10%	3%
Transportation and warehousing		
Air	67%	17%
Rail	67%	17%
Transit	67%	17%
Information (Published, broadcast)	0%	0%
Finance	0%	0%
Professional and business services	0%	0%
Education/healthcare		
Education	0%	0%
Healthcare	-15%	-4%
Arts/entertainment/accommodation/food		
Arts and recreation	80%	20%
Accommodation	80%	20%
Food service	80%	20%
Other services except government	5%	1%
Government		
Federal	0%	0%
State and local	0%	0%

Source: Congressional Budget Office

EU scenario: 11.3% decline in overall demand

The European Commission applied the same assumptions as the CBO study for the decline of demand in individual sectors and fed them into their model for the European economy and estimated an 11.3% overall decline in demand.

Table 9: EU-25 assumed decline in demand by industry in event of avian flu pandemic (%)

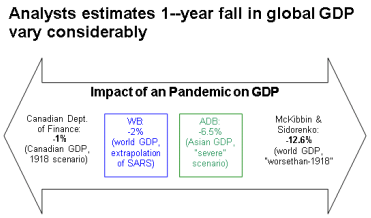
Industry sector	Decline
Agriculture	-10
Forestry	-10
Fishing	-10
Mining and quarrying	-10
Manufacturing	-10
Electricity, gas and water supply	0
Construction	-10
Sales, maintenance and repair of motor vehicles/motorcycles, retail sale of automotive fuel	-10
Wholesale trade and commission trade, except of motor vehicles/motorcycles	-10
Retail trade, except for motor vehicles/motorcycles, repair of personal and household goods	-10
Hotels & catering	-80
Inland transport	-67
Water transport	-67
Air transport	-67
Supporting and auxiliary transport activities, activities of travel agencies	-67
Communications	0
Financial intermediation, except insurance and pension funding	0
Insurance and pension funding, except compulsory social security	0
Activities auxiliary to financial intermediation	0
Real estate activities	-5
Renting of machinery and equipment	0
Computer and related activities	0
Research and development	0
Legal, technical and advertising	0
Other business activities	-5

Table 9: EU-25 assumed decline in demand by industry in event of avian flu pandemic (%)

Industry sector	Decline
Public administration and defence, compulsory social security	0
Education	0
Health and social work	15
Other community, social and personal services	-80
Private households with employed services	0
Total	***-11.3***

Source: European Commission DG for Economic and Financial Affairs

Exhibit 6: Ests. Of 1Y fall in global GDP vary widely



Source: WHO

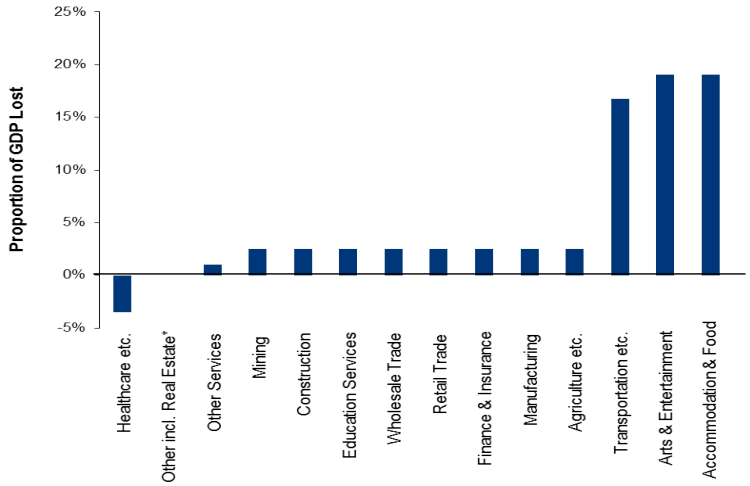
Sector impacts

Beneficiaries of the fight against pandemics would include healthcare, pharmaceuticals, life sciences and diagnostic tools, personal and protective equipment providers, as well as clinical sanitation. There would also be a positive knock-on impact on sectors that provide services within the home because people are more likely to stay in their dwellings and avoid social contact whether out of necessity or fear.

Travel, transport and leisure sectors would be hardest hit as people decrease non-essential social contact. This would include travel agencies, airlines, rail, buses, general transport, malls, casinos, restaurants, hotels, and other public entertainment providers. Certain labour-intensive industry could also be affected especially hard due to absenteeism and business disruptions.

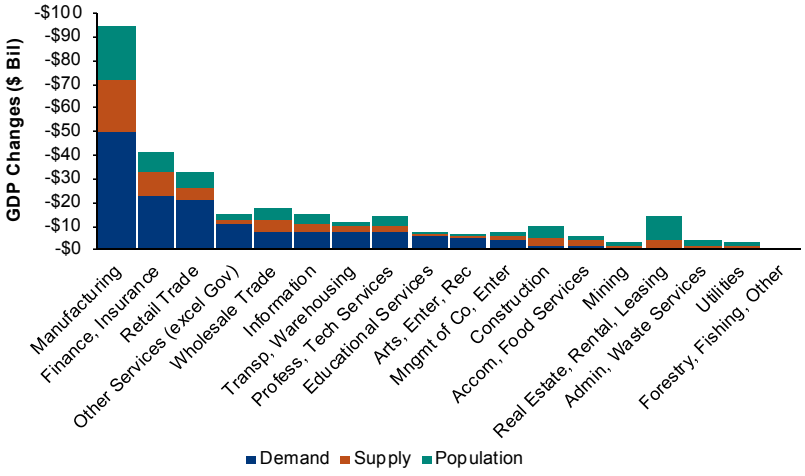
Insurers and reinsurers dealing with health, commercial property/casualty, life, property, reinsurers, and retrocessional programs would be negatively impacted by mortality and morbidity claims, adverse impacts on asset portfolio, employee absenteeism, and secondary insurance claims from business disruptions. On the other hand, annuities sellers would be positively impacted as their payments are cut shorter and their longevity risk goes down.

Chart 8: Estimated proportion of GDP Lost in USA by industry



Source: Lloyd's based on Trust for American Health

Chart 9: Average total GDP losses by shock and industry, year 1



Source: Department of Homeland Security

Severe pandemic poses global financial risks

The severity of a pandemic is determined by a combination of factors including attack and fatality rates, duration, behaviour and preparedness of households and companies as well as the capacity and preparedness of healthcare systems. A severe pandemic could result in high levels of illness and death; disruptions on the supply side (high absenteeism, people asked to stay at home, caring for sick relatives, fear of being exposed); and disruptions to transport, trade, payment systems, utilities, and increased bankruptcy risk for vulnerable companies. Demand could also contract sharply with consumer spending falling and investment being put on hold (source: IMF).

Financial repercussions could exacerbate economic impact

Financial repercussions could exacerbate the economic impact of a severe pandemic, with the IMF outlining some of the potential global economic and financial impacts:

- **Open economies could be vulnerable to deterioration in current account balances**: tourism could decline and be slow to recover; exports could suffer from trade and transport restrictions and lower global demand and supply disruptions; imports may rise because of higher need for medical goods and services.
- **A temporary increase in risk aversion is highly likely** and would lead to a surge in demand for liquidity, notably for cash and low-risk assets.
- **This "flight to quality"** would lead to temporary declines in asset prices and widening of credit spreads, for corporations and EMs.
- **Commodity prices could decline** reflecting peaking aggregate demand, but this could be offset by potential supply disruptions for commodities such as oil.
- **Asset price declines could impact the balance sheets** of some financial institutions under stress.

- **Temporary reduction in net capital flows to EMs** off the back of capital flight from residents, major investments being postponed and/or a shift in risk preferences and modest portfolio outflows in markets where equities are relatively highly priced, with weak public finances, or with current accounts dependent on commodity prices and export of services. Net flows to EMs might decline as a result of operational disruptions in the financial system, a loss of confidence in more vulnerable countries, and a rapid shift in risk preferences. There is also a possibility of a severe balance of payments scenario.

- **Operational risks could challenge the global financial system** with high absentee rates without adequate contingency plans resulting in disruptions of critical functions and services (e.g. payments, clearing, settlement, trading). ICT systems and infrastructure might also be disrupted – and a "spillover effect" across countries is possible.

- **Market operations could become more disorderly** in the case of a breakdown in trading infrastructure (source: IMF)

The inflation unknown

One major unknown is the macro effects of interest rates and inflation. Some experts suggest that when production is scaled back, the shortage of goods creates inflationary pressures. But that might not occur if the supply cutback were met by a fall in demand as people shopped less.

Investment risks, flight to quality & asset bubble

Many experts expect a "flight to quality" as investors switch from perceived risky assets to safer assets such as government bonds – which could in turn create an asset bubble (source: Lloyd's):

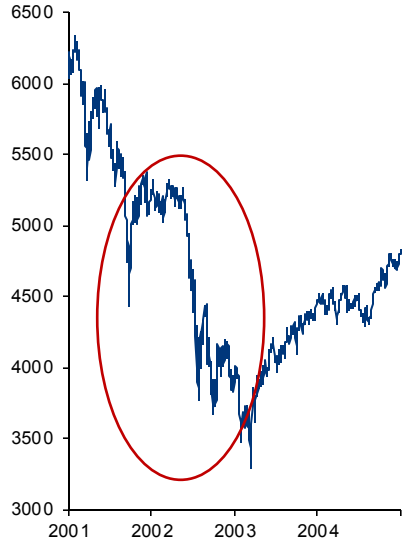
- Many equity sectors adversely affected

- Corporate bond spreads may widen vs. risk-free rates and interest rates would fall if there is a flight to quality

- Liquidity may be affected, which could impact short-term, claim-paying ability

- Just-in-time global supply chain models could mean adverse impacts for supply chains and knock-on effects throughout the economy resulting in shortages and backlogs (Source: Lloyd's)

Chart 10: Impact of loss of confidence on stock markets post 9/11 terrorist attacks



Source: Datastream, BofA Merrill Lynch Global Research

Effect on markets of previous pandemics is unpredictable

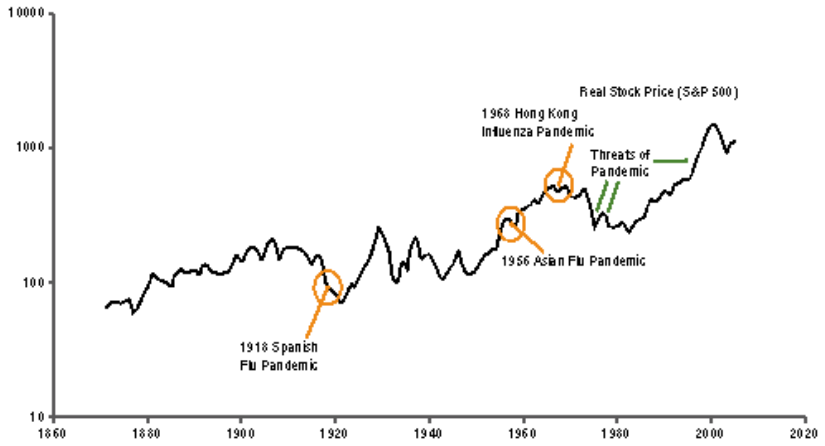
Fidelity examined the effects of historic pandemics on stock-market performance and found that equity markets react unpredictably to the unknown; that such events need to be viewed in parallel with other prevailing market conditions; and it is hard to mitigate the effects of events such as pandemics or war. Among their specific findings:

- **Spanish Flu pandemic of 1918**: Stock-market returns for 1918 are hard to obtain, and would have been affected by the end of the First World War (1914-18). The S&P 500 Index can be tracked back to 1871; it fell by 24.7% in 1918, and rose by 8.9% in 1919. The performance of the UK equity market can be tracked back to 1900; it rose by 25.4% in 1918 and by 27.0% in 1919.

- **Asian Flu pandemic of 1957**: The S&P 500 Index rose by 24.0% in 1957 and by 2.9% in 1958. In nominal terms, the UK equity market fell by 5.8% in 1957, and rose by 40.0% in 1958.

- **Hong Kong Flu pandemic of 1968**: S&P 500 Index rose by 12.5% in 1968 and by 7.4% in 1969. In nominal terms, the UK equity market rose by 57.5% in 1968, and fell by 15.6% in 1969 (Source: Fidelity).

Exhibit 7: S&P500 actual real stock price



Source: Fidleity, S&P 500: US Data http://www.econ.yale.edu/~shiller/data.htm

Economic activity would likely recover quickly

Once the pandemic has run its course, economic activity should rebound relatively quickly with the pace of recovery depending on business and consumer confidence, the speed of resumption of global trade, and the recovery of asset prices. Countries with weak fiscal and health systems would likely be more exposed and affected (i.e., lack of financial resources and capacity to purchase drugs/vaccines, treat victims in a timely manner, and provide for health security) (source: IMF).

Impacts on pension funds

A severe pandemic could mean sudden changes in liability for pension funds with Mercer HR Consulting outlining the following potential impacts:

- Short-term period of difficulty followed by a reduction in liabilities as a large number of participants/members are removed and thus liabilities reduced;
- Sudden increase in sickness and liability could create staffing issues, and impact the waiver of premiums;
- Financial market downturn could mean increased contribution rates, higher accounting pension expense, larger deficit on balance sheets, and increased guaranty levies (Source: Mercer HR Consulting)

Table 10: Potential impact of a pandemic on pension plans

Plan design	Potential impacts	Sample countries
Lump sum plans	Large cash outflows	Greece, Italy, Japan, Korea, Mexico, Taiwan, Turkey
Death benefits paid directly by the pension funds	Decreased funding level or increased insurance premiums	Belgium, UK
Funded plans	Decreased funding level and increased employer contributions	Canada, Ireland, Japan, Netherlands, UK, US
Minimum investment guaranteed return	Increased employer contributions	Austria, Belgium, Switzerland

Source: Mercer HR Consulting

"The biggest driver of the economics of pandemics is not mortality or morbidity but risk aversion, as people change their behavior to reduce their chance of exposure… People don't go to their jobs, and they don't go to shopping malls. There can be a huge decrease in consumer demand, and if (a pandemic) continues long enough, it can affect manufacturing." - Dr. Dennis Carroll, Director of USAID's programs on new and emerging disease threats.

20-60% abstenteesim rates at the height of each pandemic wave

Risk aversion is #1 impact on human behaviour

The majority of the economic losses would come not from sickness or death but from what the World Bank calls "efforts to avoid infection: reducing air travel … avoiding travel to infected destinations, and reducing consumption of services such as restaurant dining, tourism, mass transport, and nonessential retail shopping." In other words, risk aversion would create most business and social disruption and be the biggest driver of the economics of pandemics as people change their behaviour to reduce their chance of exposure. Higher rates of illness and absenteeism, decreased productivity and pressure on critical infrastructure and essential services could have major impacts on employment levels and corporate health – as well as the larger economy, especially if a pandemic were to last 1-2 years.

- **Increased absenteeism** by sick workers and those wishing to reduce the risk of contracting illness in the workplace (prophylactic absenteeism) (source: Vertikios et al.). Organisations could expect absenteeism rates of 20-60% for periods of two to four weeks at the height of each pandemic wave, with each wave lasting three to eight weeks. Factors like travel restrictions, quarantines, illness, caregiving responsibilities, and death care could have impacts across all levels of organisations (Source: Mercer HR Consulting).

- **Restrictions on movement/mobility** as governments step up containment measures when there is evidence of increased human-to-human transmission (i.e. border controls, isolating the infected, quarantining those who have had contact with infected persons). International travel could cease with rigid quarantine procedures preventing or delaying travel; bans on public gatherings, the closure of cinemas and cancellation of concerts, sporting events and shutdown of schools (Source: Mercer HR Consulting).

- **Consumer confidence would decline** due to uncertainty and fear, leading to reduced spending as people stay at home to avoid infection. This would particularly impact sectors reliant on face-to-face contact such as tourism, transport and retail (source: Vertikios et al. 2011, James & Sargent 2006).

- **Psychological impacts on attitudes to risk** could be large as evidenced by the SARS epidemic, e.g., 50% of surveyed respondents in Taiwan wore a mask at the height of the outbreak, and air travel and accommodation bookings were also affected (source: Vertikios et al. 2011, James & Sargent 2006).

Breakdown of law & order

Levels of fear and panic could increase in line with the severity of a pandemic in terms of infection and mortality rates – and could be exacerbated by absenteeism among the police, looting, collapse of just in time production, food and goods shortages etc.

Pharma, healthcare & life sciences

See also Derik De Bruin and team's Life Sciences & Diagnostic Tools: Pandemics: Tools & diagnostics at the forefront of the fight 24 September 2014

The most immediate impact of a pandemic would a surge in demand for medical services, which the US Congressional Budget Office estimates to rise by 15% in a sever pandemic, and a 4% increase in a mild case. Hospitals, clinics, and doctor's offices would be overwhelmed as demand overshoots capacity.

In the US, 90mn residents would become ill in a moderate or severe pandemic, with 45mn requiring outpatient care (source: US Department of Health and Human Services). 865,000 would require hospitalization in a moderate scenario, and 9.9mn in a severe situation. ICU care would be needed for around 65k individuals in a moderate and 1.5mn in a severe. Ultimately 209,000 would die in a moderate case and 1,903,000 in a severe pandemic (source: Smith Group).

Without government mitigation, the direct cost to US healthcare facilities including new and temporary facilities would be US$80bn (source: Department of Homeland Security). The US healthcare system will be overwhelmed in 7-10 weeks of time, and will turn away 3-4mn patients (source: Department of Homeland Security). At the same time, the ability of healthcare providers to maintain strict infection control would be challenged.

Vaccines, antivirals, and antibacterial products are the first lines of action, and are experiencing high growth as underpenetrated emerging market nations catch up their stockpiles. WHO recommends that governments have an antiviral stockpile for at least 25% of its population in order to reduce and delay hospitalization (source: Congressional Budget Office, Roche). Currently, only 85 governments have pandemic antiviral stockpiles, with a cumulative stockpile only sufficient to treat less than 5% of the population (source: Roche). The antiviral market is expected to grow at a 7% CAGR from US$28bn in 2013 to US$46bn in 2020 (source: EvaluatePharma). The US$23bn vaccine market is likewise expected grow to significantly to US$100bn by 2025, with more than 120 new products in the pipelines (source: WHO).

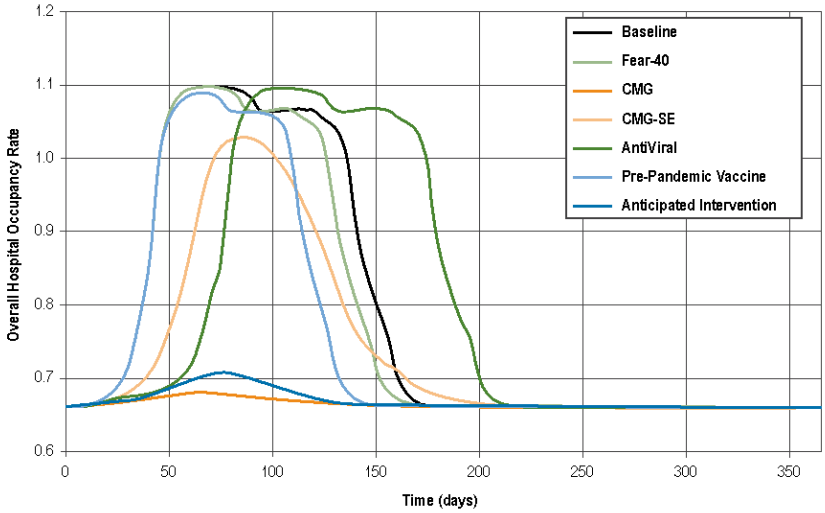
Many life sciences tools are pivotal to the diagnosis and monitoring of pandemic threats. For instance, affected people who not diagnosed timely or those who fear going into isolation, are a major factor fueling the Ebola outbreak in West Africa. Hence, point-of-care testing will be needed in the future for the rapid identification and treatment of Ebola and other infectious diseases. New technologies in pathogen genome sequencing enables scientists to reconstruct the whole history of a pathogen found in an outbreak, from tracing the source to revealing transmission routes, and identify common mutations close to "real-time" in order to help guide better clinical judgment and treatment decisions.

Personal protective equipment (PPE) and clinical waste management will be critical for containment in pandemic scenarios, especially for highly contagious diseases (source: Doctors Without Borders). WHO's mandatory PPE include - impermeable gown, mask, eye protection and double gloves or heavy duty gloves, rubber boots or closed puncture or fluid resistant shoes and overshoes (source: WHO). Ensuring adequate and secure removal of clinical waste would be critical in minimizing the spread of the disease.

Spike in healthcare demand could make up GDP losses elsewhere

Healthcare industries, at least in the short to medium-term, would experience a spike in demand. The estimated demand-side impacts are estimated to sum to about 2% of GDP (source: Congressional Budget Office).

Exhibit 8: Simulated national hospital occupancy rate (required beds/staffed beds)



Source: Department of Homeland Defense

90mn US residents ill, 1.9mn deaths

In a study done by the US Department of Health and Human Services, it was estimated that 90mn US residents would become ill in a moderate or severe pandemic, with 45mn requiring outpatient care. 865,000 would require hospitalization in a moderate scenario, and 9.9mn in a severe situation. ICU care would be needed for around 65k individuals in a moderate and 1.5mn in a severe. Ultimately 209,000 would die in a moderate case and 1,903,000 in a severe pandemic (source: Smith Group).

US$80bn of healthcare costs in the US

Without government mitigation, the direct cost to US healthcare facilities would be US$17-19bn. This would encompass the direct cost of care for the pandemic itself. If we include new or temporary facilities, this number would jump to US$80bn. The predicted GDP losses could be up to US$100bn in the first year, independent of the direct healthcare costs. (source: Department of Homeland Security).

Table 11: Hospitalization costs

	Median	Mean	Deaths	Routine Discharge
Pneumonia	$5,329	$8,127 +/- $111	3.69 +/- 0.07%	62.11 +/- 0.42%
Influenza	$3,415	$5,341 +/- $186	0.99 +/- 0.13%	77.47 +/- 0.93%
Respiratory Failure	$12,260	$21,298 +/- $533	19.73 +/- 0.35%	33.13 +/- 0.67%
Bacteria Infection	$5,881	$12,419 +/- $748	2.74 +/- 0.37%	69.64 +/- 1.79%

Source: National Inpatient Sample (NIS) from Healthcare Utilisation Project (HCUP), University of Pittsburgh

Table 12: Summary of US healthcare costs during various pandemic scenarios

	Scenario						
Factors	Baseline	Fear-40	CMG	CMG-SE	Antivirals	Prepandemic Vaccine	Anticipated
Number Illnesses	74 M	61 M	1.2 M	28 M	69 M	39 M	2.6 M
Number Hospitalized	8.1 M	6.6 M	140,000	3.0 M	7.6 M	4.2 M	280,000
Number Deaths	1.5 M	1.2 M	25,000	550,000	1.4 M	780,000	52,000
Peak Death Rate (per hour)	1,700	1,500	16	340	1,400	930	32
Day of Peak Death Rate	69	66	61	81	105	63	70
Cost of Healthcare	$81 B	$68 B	$1.7 B	$35 B	$50 B	$79 B	$9.0 B

Source: Department of Homeland Security

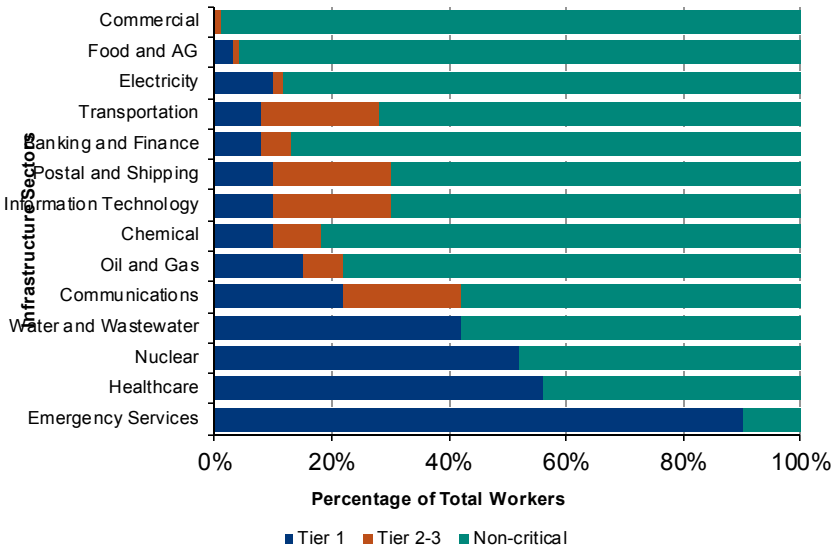
Surge capacity: demand would far outstrip supply

If we take the severe case in which 5-10mn people in the US need to be treated by hospitals, the demand would far exceed capacity. Currently, the US has around 970,000 staffed hospital beds and 100,000 ventilators, with 75% of them in use on any given day. As a result, shortages would occur in critical areas of the hospital such as ventilators, critical care beds, and drugs (source: Congressional Budget Office). The US healthcare system would be overwhelmed in 7-10 weeks of time, and would turn away 3-4mn patients (source: Department of Homeland Security). At the same time, the ability of healthcare providers to maintain strict infection control would be challenged.

Healthcare and emergency staff critical pillars

Absenteeism and uncertainty in the pharmaceuticals and healthcare supply chain would cripple the entire sector in the severe outbreak (source: OECD 2011). The NIAC considers 90% of EMT workers as critical and over 50% of healthcare workers as critical. As the demand for care rises, we may see healthcare providers contract the virus or avoid work out of fear. Given workers in the healthcare industry are more likely to come in contact with symptomatic people, they could be more likely to use distancing measures versus the rest of the population (souce: Department of Homeland Security). Surge capacity would be a concern for healthcare personnel such as nurses, epidemiologists, and lab technicians (source: Congressional Budget Office).

Chart 11: NIAC assessment on criticality of workforce in US by CI/KR sector



Source: Department of Homeland Security

Secondary hospitalizations

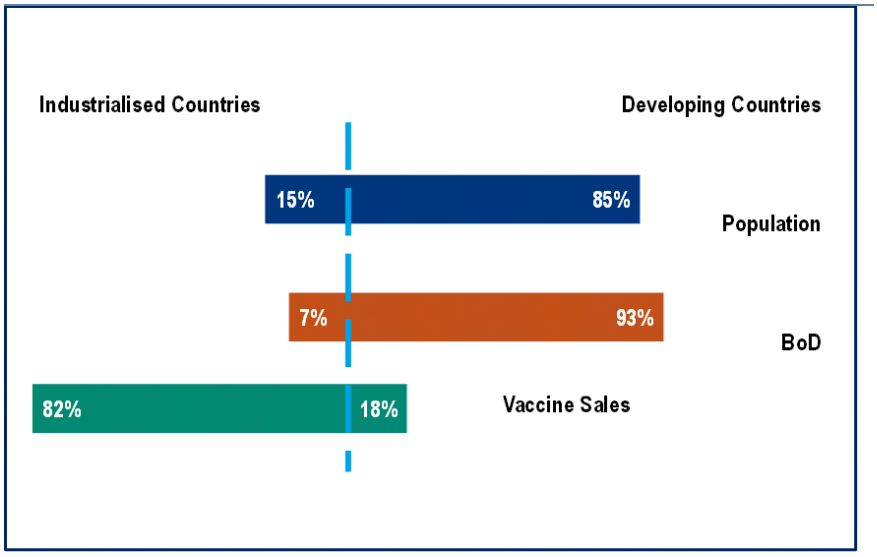
Infected victims can subsequently have secondary hospitalizations that are not directly connected to the infection itself:

- Stress-induced co-morbidity exacerbations
- Misdiagnosed patients
- Worried well, people who believe they have symptoms or fear

Vaccines are first line of defence

Vaccines exist for many infectious pandemic diseases such as influenza, measles, smallpox, etc. and immunizing the population would be an important part of prevention. A lot of the developing nations are under-served given 85% of the global population are in developing countries, but they only comprise 18% of vaccine sales. Nonetheless, the gap is closing and the emerging markets has been a key growth driver (source: WHO).

Exhibit 9: Vaccine market breakdown



Source: WHO

Could grow to be $100bn market by 2025

While the vaccine market only makes of 2 or 3% of the total pharmaceuticals markets, it has experienced a CAGR of 10-15% since 2000 versus 5-7% for the broader industry. The WHO expects the market to grow to US$100bn by 2025. There are more than 120 new products in the pipelines, of which 60 are important for developing countries (source: WHO). The net present value of the industry's R&D pipeline grew 46% to be at US$418.5 2013 versus the year prior (source: EvaluatePharma). UNICEF has been the largest single buyer of vaccines, making up for 50% of global sales in volume, with other large buyers being governments, and NGOs (source: WHO).

Table 13: Top 10 Companies & Total Worldwide Vaccine Sales 2013-2020

	Sales $m 2013	2020	CAGR 2013-20	Market Share 2013	2020
1 Sanofi + 50% Sanofi Pasteur MSD	5518	8805	7.0%	21.6%	21.3%
2 Merck & Co + 50% Sanofi Pasteur MSD	5766	8167	5.0%	22.6%	19.8%
3 Pfizer	3974	7808	10.0%	15.5%	18.9%
4 GlaxoSmithKline	5351	7412	5.0%	20.9%	17.9%
5 Novartis	1416	2363	8.0%	5.5%	5.7%
6 Novavax	-	946	n/m	n/m	2.3%
7 Johnson & Johnson	346	913	15.0%	1.4%	2.2%
8 Emergent BioSolutions	247	639	15.0%	1.0%	1.5%
9 CSL	434	464	1.0%	1.7%	1.1%
10 Astellas Pharma	350	414	2.0%	1.4%	1.0%
Top 10	23401	37929	7.0%	91.5%	91.8%
Other	2166	3391	7.0%	8.5%	8.2%
Total Industry	25567	41320	7.0%	100.0%	100.0%

Source: EvaluatePharma

Supply delays in surge

The H1N1 outbreak of 2009 showed vulnerabilities in the manufacturing process of vaccines. The H1N1 seed strains grew slowly in eggs and larger inocula were needed in the scale-up process (source: OECD 2011). This showed that there could be significant supply constraints when an actual pandemic outbreak occurs.

Antiviral drugs are first line of flu treatment

Another key strategy for governments of most developed countries for flu pandemics is the purchase and stockpiling of antiviral drugs to prevent infection and treat illness. There has only been two drugs antiviral drugs that have shown promise in treating avian flu – oseltamivir and zanamivir. Oseltamivir is marketed under Tamiflu by Roche, and Zanamivir as Relenza by GlaxoSmithKline. The two drugs have shelf-lives of 3Y and 5Y respectively. Countries such as Japan, UK, France, Norway, the Netherlands, and New Zealand are pursuing the stockpiling approach (source: Congressional Budget Office).

US$46bn market by 2020

The antiviral market is expected to grow at a 7% CAGR from US$28bn in 2013 to US$46bn in 2020. The market is also highly concentrated, with the top 10 companies taking 93% market share (source: EvaluatePharma).

Table 14: Top 10 companies & worldwide anti-viral sales 2013-2020

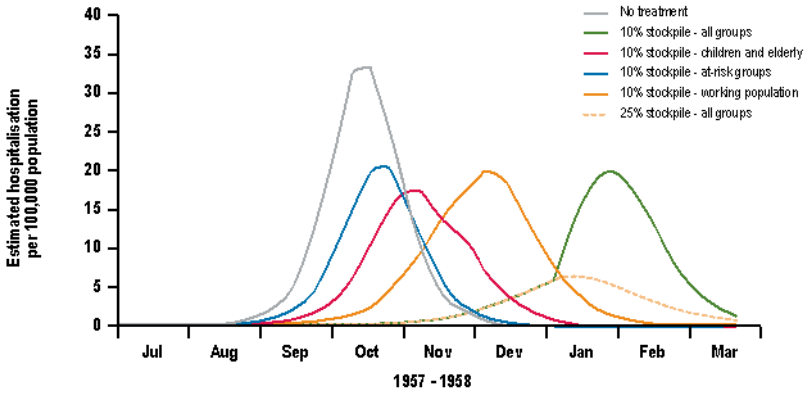
	Sales $m		CAGR	Market Share	
	2013	2020	2013-20	2013	2020
1 Gilead Sciences	9340	21797	13.0%	33.5%	47.8%
2 GlaxoSmithKline	3212	5657	8.0%	11.5%	12.4%
3 AbbVie	2232	3425	6.0%	8.0%	7.5%
4 Merck & Co	2281	3167	5.0%	8.2%	7.0%
5 Johnson & Johnson	2828	2607	-1.0%	10.2%	5.7%
6 Bristol-Myers Squibb	3330	1832	-8.0%	12.0%	4.0%
7 Sino Biopharmaceutical	618	1393	12.0%	2.2%	3.1%
8 Achillion Pharmaceuticals	-	595	n/m	n/m	1.3%
9 AstraZeneca	617	583	-1.0%	2.2%	1.3%
10 Roche	1550	578	-13.0%	5.6%	1.3%
Top 10	26008	41635	7.0%	93.4%	91.4%
Other	1833	3925	11.0%	6.6%	8.6%
Total Industry	27841	45560	7.0%	100.0%	100.0%

Source: EvaluatePharma

Recommended 25% of population stockpile

WHO recommends that governments have an antiviral stockpile for at least 25% of its population. This would significantly reduce and delays hospitalization (source: Congressional Budget Office, Roche). Currently, 85 governments have pandemic antiviral stockpiles, with a cumulative stockpiles only sufficient to treat less than 5% of the population (source: Roche).

Exhibit 10: Stockpiling reduces delays significantly

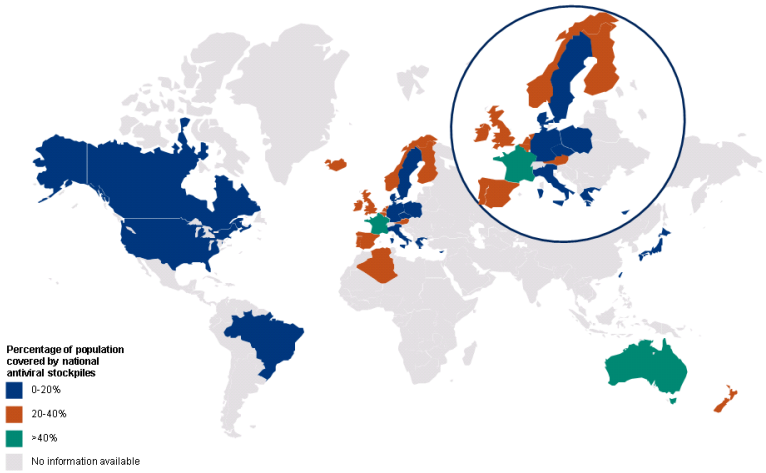


Source: Roche

Demand would exceed production capacity

By the end of 2005, the US Strategic National Stockpile had bought up 4mn Tamiflu treatments and 84,000 Relenza treatments. Demand for Tamiflu by governments and private entities had far exceeded Roche's production capacity in 2006 and the firm temporarily suspended shipments to the US in October of that year to prevent hoarding (source: Congressional Budget Office). Roche also halted shipments to certain wholesalers until the influenza season started, and worked with health authorities to restrict dosage (source: Roche).

Exhibit 11: % of population covered by national antiviral stockpiles

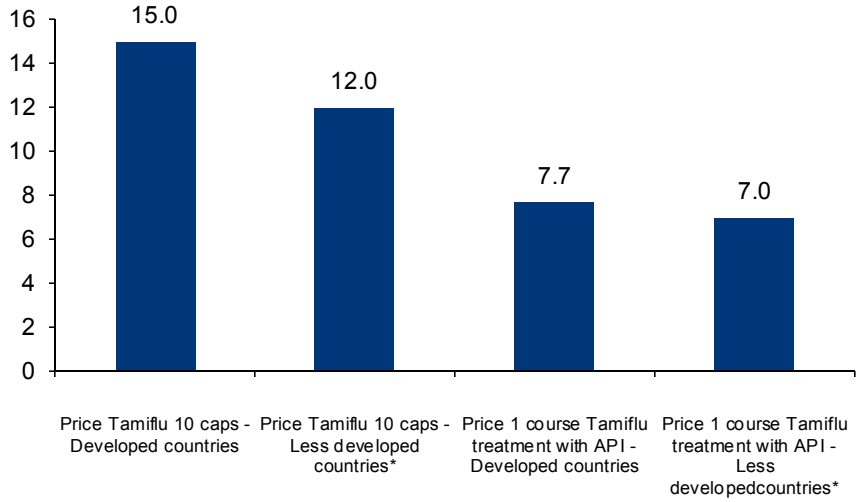


Source: Roche

Tiered pricing depending on income of country

Many pharmaceutical companies have also adopted a tiered pricing system for antivirals during a pandemic scenario. Roche for example charges 10-25% more for developed countries versus less developed countries. Prices are also cut dramatically for pandemic scenarios, 7-15EUR versus 20-51EUR normally. In order to remove intellectual barriers, the company also did not file for Tamiflu patents in the world's poorest countries (source: Roche).

Chart 12: Tamiflu cost across regions (€) during pandemic scenarios



Source: Roche

Companies and public entities work together in pandemic scenarios

Roche and WHO have a partnership, in which Roche will be called upon to increase production capabilities and reprioritize orders when WHO declares an official pandemic. Once declared, Roche will fill Tamiflu orders as follows:

- Deliver WHO rapid response stockpiles donated by Roche to WHO
- Fulfilment of existing pandemic orders from both governments and other groups
- Increase rapid response effort for containment in collaboration with WHO and other international agencies (source: Roche)

Biotechnology: New drugs for bad bugs; a gram negative primer 20 June 2014

Drug resistance is of a concern

Antiviral drug resistance is an area of intense study and controversy. The WHO has drawn specific guidelines concerning its use in seasonal influenza and pandemic scenarios according to the observed resistance of the virus to the known antiviral agents (source: OECD 2011). At the same time, antibiotic resistance is also an area of major concern. In 2004, the Infectious Diseases Society of America (IDSA) released a report stating that 70% of 90,000 deaths from bacterial infections were attributable to antibiotic resistant strains. Levels of resistance are expected to increase, and the BioTrends research group stated that two-thirds of surveyed hospital-based infectious disease specialists reported increases in the incidence of infections due to drug-resistant gram negative pathogens in the past two years.

Table 15: The antiviral susceptibilities of circulating viruses are as of January 2010

	Oseltamivir	Zanamivir	M2 inhibitors[a]
Pandemic (H1N1) 2009	Susceptiblea	Susceptible	Resistant
Seasonal A (H1N1)[b]	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant

Table 15: The antiviral susceptibilities of circulating viruses are as of January 2010

	Oseltamivir	Zanamivir	M2 inhibitors[a]

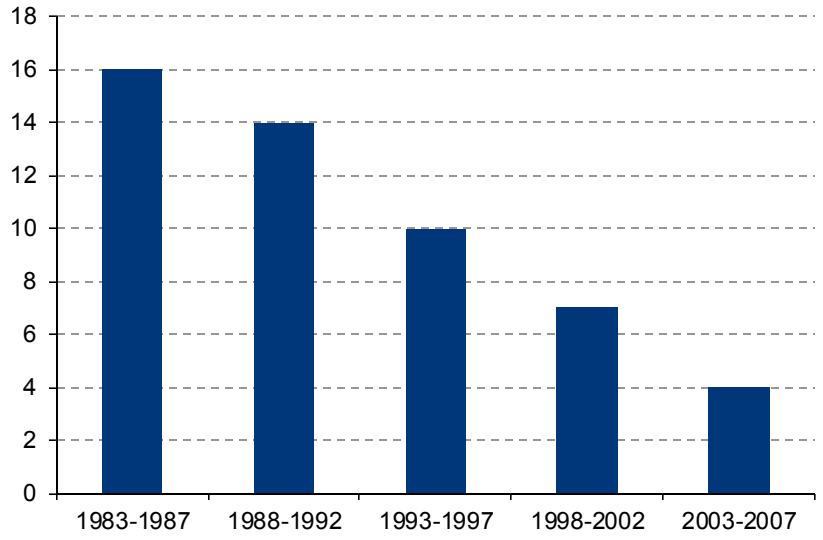
a. Amantadine and rimantadine
b. Seasonal A (H1N1) refers to the human influenza A (H1N1) viruses that were circulating prior to the introduction of pandemic influenza A(H1N1) 2009 virus and which continued to circulate during 2009.

Source: OECD 2011

Smaller companies involved

In recent decades there has been a lack of new antibacterial therapies approved, due in part to high costs of drug development, complexity of designing clinical trials, as well as profit duration concerns due to the potential of new resistance Currently, the pipeline for new antibiotic agents for large pharmaceuticals is also fairly sparse (source: CDC, OECD 2011). However, our Biotech research team has seen a significant increase in antibiotic R&D from smaller companies.

Chart 13: Total number of new antibacterial agents approved



Source: Spellberg, et. Al., CID Jan 2008

Table 16: Antibiotic company valuations

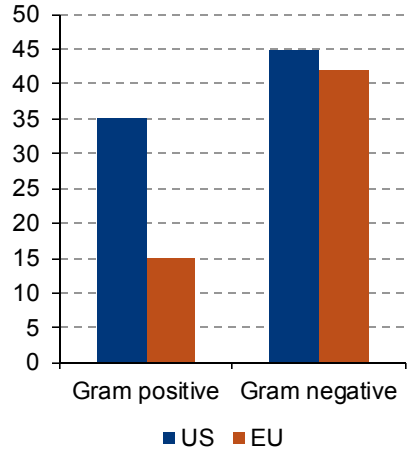
	Company	EV ($mn)	Antibiotic platform	Phase*
CBST	Cubist	5461	Cubicin, Dificid, Sivextro, ceftolozane/tazobactam, surotomycin, CB-618, gyrase	2 marketed, 2 filed, 1 phase 3, 2 pre-clinical/phase 1
	Trius	704+105 CVRs	Sivextro, gyrase	Phase 3, pre-clinical
	Optimer	555+250 CVRs	Dificid	Marketed
MDCO	Medicines Co	1682	Minocin IV/RPX-602, carbavance, next gen platform	Marketed/sNDA prep, phase 3, pre-clinical
	Rempex	104+334 milestones	Minocin IV/RPX-602, carbavance, next gen platform	Marketed/sNDA prep, phase 3 ready, pre-clinical
INSM	Insmed	657	Arikace	Phase 3
DRTX	Durata	429	Dalvance	Approved
AKAO	Achaogen	401	Plazomicin, LpxC inhibitors	Phase 3, pre-clinical
CEMP	Cempra	282	Solithromycin, Taksta	Phase 3, phase 2
TTPH	Tetraphase	256	Eravacycline, TP-271, pseudomonas program	Phase 3, IND-enabling, 2 pre-clinical
	Melinta	private	Delafloxacin, radezolid, RX-04	Phase 3, phase 2, phase 1

Source: Bloomberg EV as of EOD 6/19/2014, BofAML Global Research, Company reports., *for acquired companies, phase at acquisition

Help from government agencies

In response to significant resistance threats from gram positive and gram negative bacteria, government agencies such as the Biomedical Advance Research and Development Authority (BARDA) are providing significant funding to support the discovery and development of new antibiotics. Antibiotic regulation and legislation initiatives to encourage development have emerged, allowing for lengthened exclusivity periods and shorter paths to approval. Today, diversified companies such as The Medicines Company (MDCO), Forest and AstraZeneca all have antibiotics in their pipelines.

Chart 14: Days of therapy (in millions)



Source: CBST, AMR, IMS

US$26bn antibiotic market currently

Annual sales of antibiotics have reached over $26bn. Gram negative pathogens are more diverse and have higher resistance levels than gram positive pathogens, and there is no standard of care for gram negative infections, like there is for gram positive (ie, vancomycin). Bacteria can be generally classified as gram negative or gram positive using a lab test that distinguishes bacteria based on the composition of the cell wall. Incidence data show that the gram negative market opportunity is larger than the gram positive market, with 80% more days of therapy. Estimates suggest at least 75-85 million days of therapy in the US and EU for gram-negative infections, versus 35 million days of therapy for gram positive infections (ie, MRSA) in the US with a significantly lower number of days of therapy in the EU. Global bacterial ICU infections were 43% gram positive and 57% gram negative (JAMA 2007). Enterobacteriaceae (including *Klebsiella* spp. and *E. coli*) is a major cause of infections in the US and EU each year. Carbapenems such as meropenem generated peak sales of approximately $1bn before going generic.

Boon for pharmaceuticals sector could be concentrated

In 2012, the US awarded US$25bn to three pharmaceutical companies. The World Bank estimates that an annual expenditure of US$3.4bn would be required in developing countries for the world to acquire a robust pandemic prevention capability (source: World Bank).

Life Sciences & Diagnostic Tools: Pandemics: Tools & diagnostics at the forefront of the fight 22 September 2014

Life sciences tools help with diagnosis and monitoring

Many life sciences tools are available to aid with diagnosis and monitoring of pandemic threats. In fact, a major factor fueling the Ebola outbreak in West Africa is shortage of diagnostic centers. Affected people are not diagnosed timely and fear going into isolation until they cannot cope with the symptoms. As a result, point-of-care testing will be needed in the future for the rapid identification and treatment of Ebola.

Genomic analysis gives better understanding

Different than standard molecular diagnostic tests which typically inspect a small number of genes, pathogen genome sequencing enables scientists to reconstruct the whole history of a pathogen found in an outbreak, from tracing the source to revealing transmission routes, and identify common mutations close to "real-time" in order to help guide better clinical judgment and treatment decisions. Companies like ILMN, TMO, and PACB are key suppliers of tools for microbial genome analysis.

Many influenza test kits available

For influenza, there are many FDA cleared test kits. Suppliers typically benefit from a strong flu season. Key vendors of molecular flu tests include CPHD, BIM,

QDEL, LMNX, and QGEN. ALR, BDX, QDEL, VIVO, and TMO chiefly supply rapid flu tests. When new flu strains emerge (e.g., H1N1), RT-PCR systems from TMO and Roche, as well as QGEN nucleic acid purification reagents, are often used as the basis of laboratory developed molecular tests. BDX, CAH, CTLT, MCK, and WST sell various syringes, needles and other medical supplies used for vaccinations.

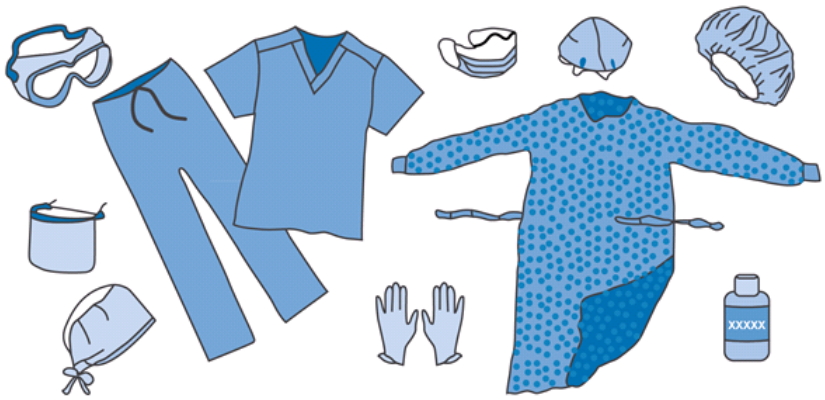
Ebola diagnostics are work-in-progress

While there is no FDA cleared diagnostic test for Ebola, infections can be diagnosed through antibody-capture enzyme-linked immunosorbent assay (ELISA), antigen detection, serum neutralization, reverse transcriptase polymerase chain reaction (RT-PCR) assay, and virus isolation by cell culture. TMO, QGEN, Roche, and BIO are key suppliers of instruments and reagents used to diagnose viral infections like Ebola. In July, the NIH awarded a three-year $2.9mn grant to Corgenix (CONX; recently acquired by Orgentec) and the Viral Hemorrhagic Fever Consortium (VHFC) to continue work on the development of an Ebola rapid diagnostic test kit.

Expect huge increase in protective wear

The demand for personal protective equipment (PPE) and other protective wear will be high in pandemic scenarios, especially for highly contagious diseases such as ebola (source: Doctors Without Borders). WHO has drawn up guidelines for healthcare workers for handling ebola cases. Mandatory PPE include - impermeable gown, mask, eye protection and double gloves or heavy duty gloves, rubber boots or closed puncture or fluid resistant shoes and overshoes (source: WHO). For a novice, the process of taking the protective wear can take as long 30 minutes (source: Doctors Without Borders).

Exhibit 12: Recommended Ebola protective wear



Source: WHO

Exhibit 13: Doctor wearing recommended Ebola protective wear

Source: Doctors without Borders

Clinical waste management will be critical

Given the highly infectious nature of certain diseases, the amount of clinical waste would be high and proper disposal would be critical in minimizing the spread of the disease. In the case of ebola, all waste must be segregated as point of generation and collected in leak-proof covered bins. Tissues or other body fluids for disposal need to be placed in clearly marked, sealed containers, and then incinerated (source: WHO). Waste volumes can also be overwhelming as seen in the case of Emory University Hospital in Atlanta, which took in two ebola patients in August 2014. According to Dr. Aneesh Mehta of Emory, they were producing up to 40 bags of medical waste per day (source: Reuters). Ensuring adequate waste management will remove unnecessary obstacles.

Insurance and Reinsurance

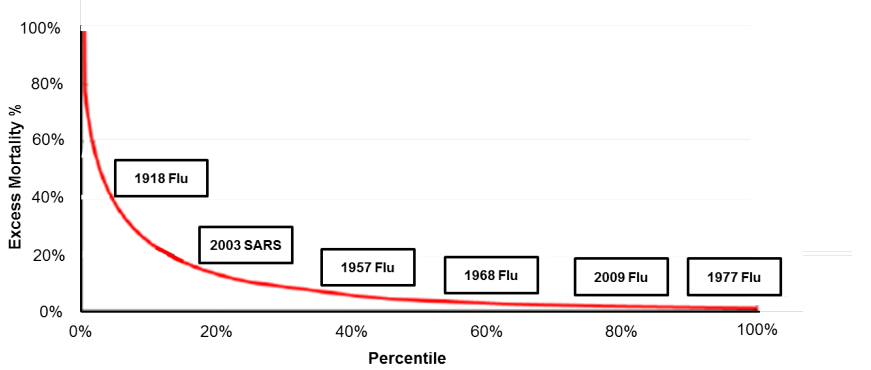
Disease-related events are the number one extreme mortality risk for life insurers, and pandemics represent the largest risk for the industry given their potential for widespread and significant effects on the global population (Source: Milliman). Issues around pandemics include – increased mortality and morbidity claims, adverse impacts on asset portfolio, employee absenteeism, and secondary insurance claims from business disruptions.

It is challenging for insurers and reinsurers to assess pandemic risk exposure because there is a lack of historical data, and simple worst case scenario approaches do not offer guidance on likelihood or possible losses. Nonetheless, there has been an uptick in risk assessment for insurances on the back of Solvency II requirements for the EU and NAIC'S Own Risk and Solvency Assessment (ORSA) for the US (source: SCOR). Most insurers use internal models with different levels of risk tolerance to Solvency II and may also develop stochastic mortality model calibrated to extreme events and specific risk characteristics of the portfolio (source: SCOR, Milliman).

The variances in assessments and analyses vary greatly, ranging from hundreds of thousands of deaths vs. millions, with costs ranging from millions of dollars to the billions (source: Smith Group). Standard & Poor's conducted a study by looking at the combined losses from health, commercial property/casualty, life, property, reinsurers, and retrocessional programs world-wide, and they estimated the worst case scenario losses at US$71.3-200bn related to an avian flu epidemic (source: Standard & Poor, Business Insurance). We believe that as much as 10-20% of mature insurance markets will be impacted.

Reinsurance, capital markets, and risk exclusion offer the biggest opportunity for diversifying the pandemic risk pool. Reinsurance is a natural risk mitigation option for insurers as reinsurers have a higher appetite for extreme mortality risk. In turn, insurer and reinsurers can transfer extreme mortality risks to the capital markets insurance-linked securities (ILS) such as extreme mortality bonds or extreme mortality swap (source: Actuaries Institute, InsuranceLinked). ILS offers the opportunity to participate in uncorrelated returns, thus bringing positive diversification effects for investors. As an alternative, insurers and reinsurers can exclude pandemic-related claims in the policy terms completely (Source: Milliman).

Chart 15: Illustrative disease model severity curve



Source: Milliman

Quantifying risk is difficult

For insurers and reinsurers looking to assess risk exposure to extreme mortality events, simple worst case scenario approach such as sum-at risk or maximum loss net of reinsurance does not offer any great guidance on likelihood or possible losses. Given there has only been three pandemics in the last century, the pool of historical data is also limited. Current ways to model extreme mortality risk ranges from actuarial approaches based on historic pandemics to more complex system models that integrate the preparedness of governments in responding to pandemics or the ability to rapidly develop vaccines (source: Milliman). There are many specific Portfolio characteristics at play, such as age-gender mix, underlying health conditions, as well as socioeconomic status (source: SCOR).

Solvency II demands more detailed analysis

Although pandemic risk has been tough to pin down, there has a heightened sense of pandemic awareness. There has been an uptick in risk assessment for insurances on the back of Solvency II requirements for the EU and NAIC'S Own Risk and Solvency Assessment (ORSA) for the US. Under Solvency II and ORSA, insurance companies must quantify their risk appetite and tolerances.

Solvency II requires entities to maintain capital to meet the Solvency Capital Requirement (SCR). SCR provides a standard formula that defines a single scenario at a 1 in 200 year level (Source: SCOR). Solvency II defines the 1/200Y scenario to be an increase in mortality rates of 1.5 per 1000 over a 1 year period. This offers a proxy of financial risk and capital requirements but doesn't offer a full picture of the overall risk distribution. Most insurers use internal models with different levels of risk tolerance to Solvency II and may also develop stochastic mortality model calibrated to extreme events and specific risk characteristics of the portfolio (source: SCOR, Milliman).

Massive variations amongst pandemic estimates

The variances in assessments and analyses vary greatly, ranging from hundreds of thousands of deaths vs. millions, with costs ranging from millions of dollars to the billions (source: Smith Group).

Australian study: life insurance <$1bn losses

A study done by the Australian Department of Health and Ageing predicted that flu pandemic would cost the Australian insurance industry less than AU$1bn and would have relatively small impact on the earnings of the parent companies. Their assumptions were as follows:

- Insurance penetration of age 20-65 – 50%
- APRA's floor for event stress charge – 1 per mille
- Average sum assured per life – US$150,000

Table 17: Pandemic scenarios for life assurance companies in Australia

Company	Market Share (Premium) 2011 based on Plan 4 Life	Est. Penetration to Australian lives	No. of Additional Insured Lives on Claim	Additional Claims (million)	Approx. Latest Earnings in the Insurance/Wealth Mgmt Group (millions)	Approx. Latest Earnings for Parent Group (million)	Direct Impact on Profitability - Insurance Group	Direct Impact on Profitability - Parent Group
A	17%	1,075,259	1,075	161	500	5,000	32%	3%
B	16%	1,012,009	1,012	152	700	700	22%	22%
Company	13%	822,257	822	123	2,000	2,000	6%	6%
D	13%	822,257	822	123	300	7,000	41%	2%
E	12%	759,006	759	114	300	5,000	38%	2%
F	8%	506,004	506	76	100	1,000	76%	8%
Other	*8%*	*506,004*	*506*	*76*				
H	7%	442,754	443	66	200	7,000	33%	1%
I	5%	316,253	316	47	3,000	3,000	2%	2%
J	1%	63,251	63	9	small	500		2%

Source: Actuaries institute

While impact on a concentrated insurance business unit or company may be large, generally the impact on the overall parent company is relatively small (source: Actuaries Institute).

US study: 200k deaths, 10mn outpatient care, $40bn losses

In a separate study done by Risk Management Solutions (RMS), a group that specializes in catastrophic risk models for the insurance industry predicted a US$40bn loss for the US insurance industry. They assumed that 35% of the US population would become clinically ill, 200,000 deaths and 10mn seeking outpatient care (source: Smith Group).

Table 18: Possible impact on US insurance industry

	Number of Deaths	Casualties	Industry Loss in Millions
Group Life	69,300	69,300	$2,678
Individual Life	72,200	7,200	$6,433
Workers Comp	280	14,100	$247
Health Insured	140,100	7,152,700	$30,523

Source: Smith Group, RMS

Fitch arrived at similar figures using a moderate impact model similar to the CDC and RMS. They estimates an avian influenza pandemic would cause around 209,000 deaths in the US and 400,000 in Europe, resulting in an increase of US$18bn in group life and reinsurance in the US and £20bn in Europe (source: Smith Group).

The extreme case: up to US$200bn in insurance and reinsurance losses

Estimates from economist Steven Weisbart of the Insurance Information Institute and Standard & Poor are much more severe. Weisbart's estimates are taken from statistical data from the 1918 and 1958/1959 flu pandemics. It encapsulates increased claims in excess of expected mortality, and includes asset deterioration from government imposed quarantines and associated decrease in attendance at public businesses such as entertainment, shopping, restaurants, and leisure. He concludes that a moderate epidemic would result in 115k deaths and a severe in 670k deaths, with a total associated cost to insurers at US$133bn. The great majority of the losses would arise from claims from the under 35 age group (source: Smith Group). A separate study by Standard & Poor's looking at the combined losses from health, commercial property/casualty, life, property, reinsurers, and retrocessional programs world-wide, put the worst case scenario losses at US$71.3-200bn related to an avian flu epidemic (source: Standard & Poor, Business Insurance).

Table 19: Weisbart hypothesis of pandemic on Group Life and Individual Life Insurance

	Moderate (1958/1968) 115,345 deaths	Sever (1918) 699,171 deaths
Group Life	$11 Billion	$54 Billion
Individual Life	$20 Billion	$79 Billion

Source: Smith Group

Mortality linked to pre-existing conditions

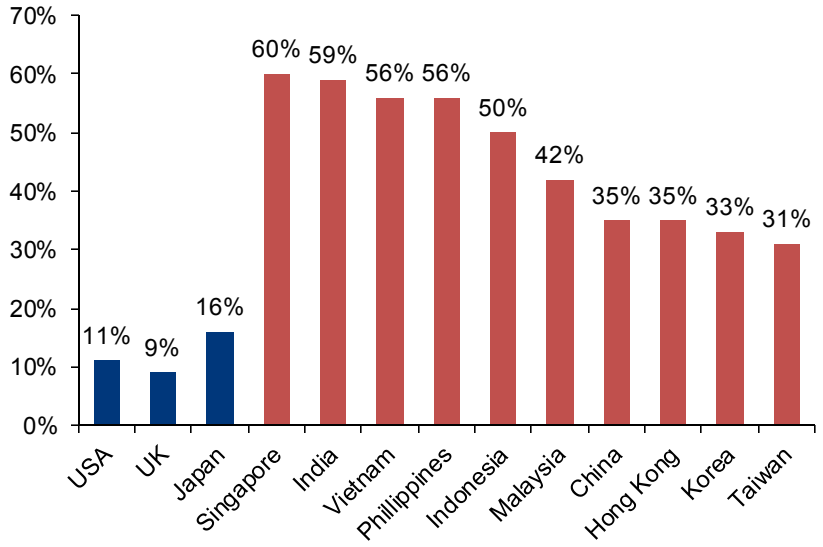
Studies have shown that there is increased risk of death from a severe infectious disease if the subject suffers from pre-existing conditions such as respiratory and cardiovascular diseases, liver diseases, diabetes, kidney diseases, neurological diseases, immune deficiency, and obesity (source: Euro Surveillance). A study performed on the H1N1 outbreak in 2009 showed that in US, 70% of individuals dying from the influenza pandemic between April and July of that year had a pre-existing medical condition. Hence, those with chronic health conditions may be predisposed to more adverse outcomes of pandemics. In applying for insurance, diseases with mortality significance are usually screened this. This means that those with insurance policies could potentially have a lower risk of pandemic mortality than the general population (source: SCOR).

Sanity check suggests a 10-20% impact (mature markets)

Do these estimates pass a sanity check? Our insurance team thinks they do. It has been suggested that a severe pandemic may infect 30% of the US population and have a 2.5% mortality rate. In this scenario, around 2m deaths could occur in the US. If we assume that 1m (50%) of those were covered by insurance (insured deaths) with an average sum insured of $150k, the total cost would be $100bn after tax. And we suppose that a more moderate pandemic may result in losses half this scale. Against a market cap of around $500-600bn for the US insurance sector, a moderate to severe pandemic could therefore wipe out 10-20% of the value from insured losses alone i.e not including financial market effects.

Of course there could be additional claims from ill health, medical and business interruption. These are very difficult to model. But against this, insurers may also be able to release reserves held on products where longevity is being insured (e.g where payments are guaranteed for life). Or in the event that a pandemic causes death but relatively short or few instances of illness (morbidity), reserves against accident and health losses may also be able to be written back. There are also huge variations in how healthcare is paid for. For instance, while 9% of medical expenses are paid out of pocket in UK, that number is 60% for Singapore (source: Prudential PLC).

Chart 16: Share of medical expenses paid out-of-pocket, %



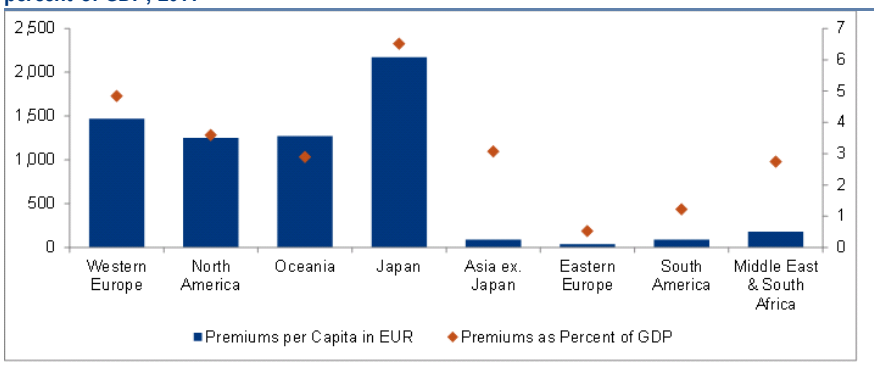
Source: Prudential PLC

It is also not clear precisely where across the sector such losses would hit. Although primary life companies in the US tend to reinsure only around 30% of the business written, we think the reinsurance share of pandemic losses would be greater than this. Primary insurers are highly likely to have meaningful

reinsurance protection against such 'tail events' – reinsurance solutions are discussed in detail below. In practical terms, this means that primary insurance companies are likely to retain only a limited portion of such risks. Once a pandemic takes hold, we think the majority of losses would likely sit with the reinsurance industry. This risk is likely to be spread across a large number of companies, as is normal practice within the reinsurance industry.

Finally in terms of linking this example to other countries and regions it is important to consider the penetration of insurance across the world. The US is one of the most highly penetrated markets globally, with approximately half of US lives insured. The UK and some European countries have similar levels of insurance penetration. But this drops sharply when considering emerging markets such as some Asian and Latin American countries. In some cases penetration is 10-20% of that found in the US, suggesting that only 5-10% of the population would be covered against death or illness. Therefore estimates of possible losses in these regions would need to be scaled accordingly to reflect lower levels of insurance.

Exhibit 14: Life insurance density and penetration: Premiums per capita in EUR and as percent of GDP, 2011



Source: Allianz

Risk transfer solutions

Capital and reinsurance markets offer the biggest opportunity for diversifying the pandemic risk pool.

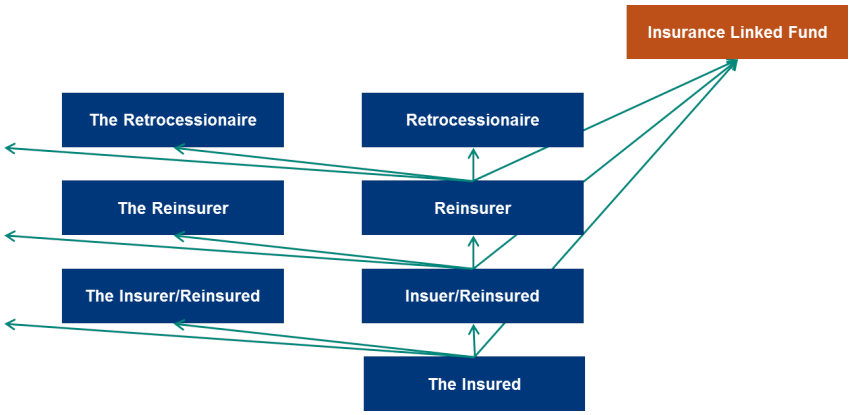
- **Reinsurance** is a natural risk mitigation option for mortality risk as reinsurers have a higher appetite for extreme mortality risk (e.g. stop-loss cover, quota-share or excess-of-loss covers), but given the high risk of pandemics and could lead to significant losses for insurers
- **Capital markets**: several insurer and reinsurers have issued mortality cat bonds to transfer extreme mortality risks to the capital markets (i.e. insurance-linked securities or ILS which offers investors the opportunity to participate in uncorrelated returns, thus bringing positive diversification effects)
- **Risk exclusions**: Excluding claims in the policy terms (Source: Milliman).

Reinsurers, first line of defence for insurers

Reinsurance insures insurance companies, which provides an alternative to capital as well has reduce the earnings volatility for insurance companies.

Reinsurance companies can then buy cover as well, which is called retrocession. Reinsurance predominantly comes in two main categories, excess of loss reinsurance (XoL) and proportional (source: InsuranceLinked).

Chart 17: Reinsurers – first line of defence



Source: Insurance Linked

Excess of loss reinsurance

Excess of loss protects insurance companies against large unexpected losses and comes in three forms – large loss at a single location (Per Risk XL), accumulation of losses from ma single event (Catastrophe XL), and accumulation of losses during a period of time (Aggregate XL).

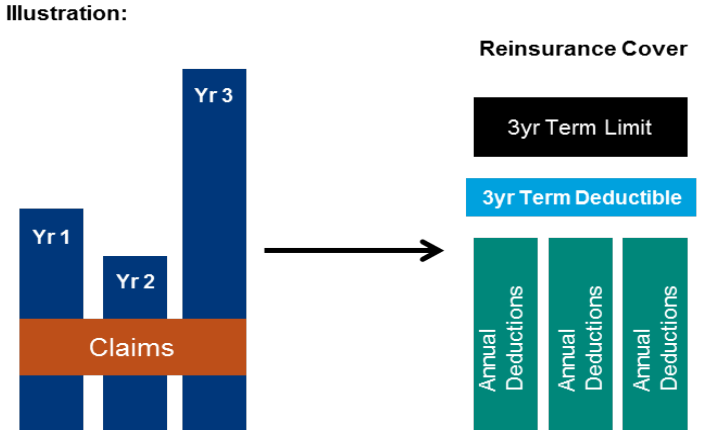
Cat XL for pandemic events

Catastrophe excess of loss reinsurance or Cat XL or Event XL is the most common type of reinsurance. The structure is typically specified in terms of X over Y in which Y is the amount of loss that is necessary to trigger the contract, with X specifying the level of maximum possible recovery (source: InsuranceLinked). In the case of a pandemic, the trigger can be an official body's (i.e. WHO) declaration pandemic state, which would constitute breaching Y level. One can aggregate claims that arise out of the pandemic event, within X consecutive days (source: Actuaries Institute).

Aggregate XL Stop Loss Reinsurance

Aggregate XL reinsurance model can cover excess mortality, disability, or medical costs over a period of time. When the aggregate cover is linked so the insurance company's gross premium income during a one year period, with a limit and deductible, this becomes an Aggregate XL Stop Loss contract. In this case, the reinsurer would cover losses deductible X dollars, up to limit Y dollars. This could also include some sort of pandemic trigger (source: Actuaries Institute).

Chart 18: Aggregate XL Stop Loss Reinsurance overview

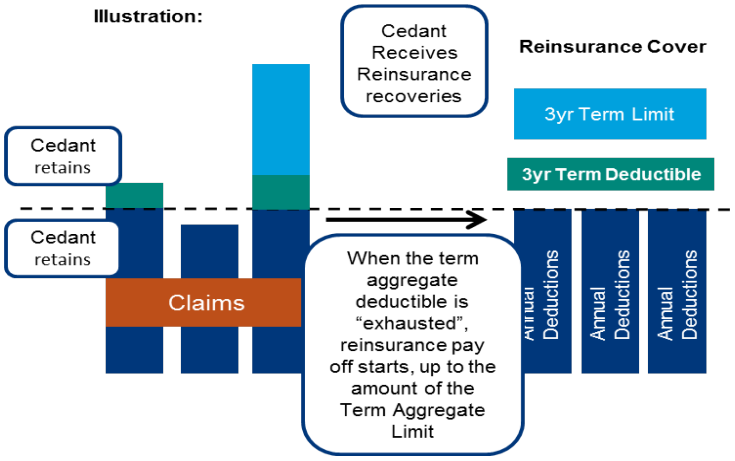


Source: Actuaries institute

In the sample model, the amount of actual claims has to be above the annual deductible in order to trigger the insurance.

Claims amount in excess of the annual deductible will first exhaust the term aggregate deductible. The cedant, or primary insurance company, will cover the claims until the aggregate deductible is exhausted. After this, the reinsurance pay off starts, and will pay out up to the amount of the Term Aggregate Limit.

Chart 19: Aggregate XL Stop Loss Reinsurance triggers



Source: Actuaries institute

Proportional reinsurance

In proportional reinsurance, the reinsurer participates in the profits and losses of the insurer, much like owning equity. This allows insurers to sell greater insurance policies on a fixed asset base, and the process is more flexible than raising new capital (source: InsuranceLinked).

Retrocession, reinsurance for reinsurers

Retrocession, the reinsurance for reinsurers, have the same structure with the primary reinsurance. The breadth is wide given it would cover anywhere in the world in any line of business. Understanding correlations within the underlying transactions is quite complex, leading to wider markings. Nonetheless, the market is significantly smaller – around 10% of the US$25bn property catastrophe reinsurance market for example (source: InsuranceLinked).

Insurance Linked Securities linking insurance risk and capital markets

Insurance linked securities (ILS) are debt instruments that insurance and reinsurance companies use to transfer insurance risk to the capital markets. The ILS market is composed of property catastrophe bonds (cat bonds), mortality bonds, and longevity bonds. The bonds would pay period coupons to the investor during the life of the bond, while the principal is at risk following a trigger even that affects the sponsoring company (source: InsuranceLinked).

Pandemics – Extreme mortality bond

Life bonds would protect insurers and reinsurers that large numbers of people die earlier due to some national or international event. In the case of pandemics, war, or natural disaster, an extreme mortality bond would help diffuse the risk from the issuing entity. Would offer multi-year coverage, or the maturity of the bond. It would lock in favourable pricing for the insurer, giving it an avenue for diversification. The legal structure of an extreme mortality bond would be similar to that on a non-life ILS (source: Actuaries Institute).

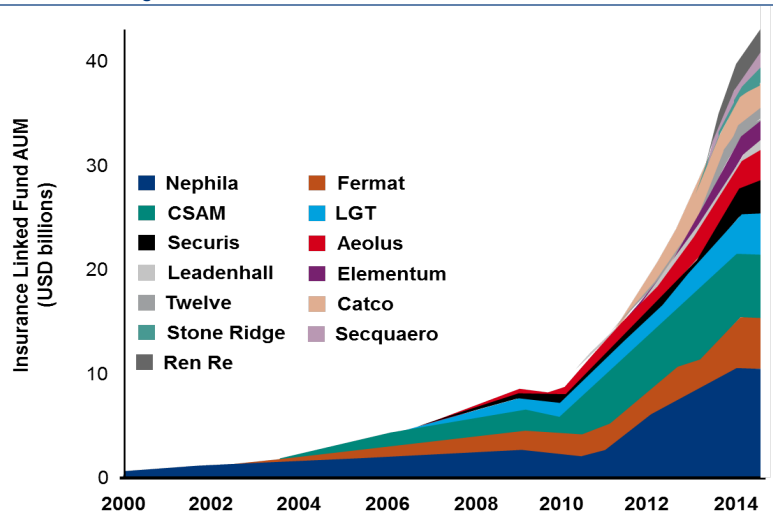
Extreme mortality swap

Extreme mortality swaps would share many similar risk attributes as extreme mortality bonds. However, the swap would have annual renewals at the reset of the swap, during which it would be open to alteration in price. This would differ from bonds in that it would target a smaller investor placement, but would entail lower costs in terms of legal and transaction (source: Actuaries Institute).

Insurance linked funds, participating at every stage

Insurance linked funds are a group of vehicles that sell insurance, reinsurance, and retrocession, but are capitalized in a way that they are tied to directly to underlying assets and not correlated to market returns (source: InsuranceLinked).

Chart 20: Estimated growth of insurance linked funds



Source: InsuranceLinked

Longevity risk, a natural hedge

A natural hedge for life insurance companies is that mortality eases longevity risk, and their annuities payment obligations will cease earlier than expected. However, this is predicated on many factors. For example, the 1918 flu pandemic

disproportionately affected those of working age and only had a mild effect on the elderly, the age group that normally would take out annuities (source: Lloyds).

Insurance will experience secondary effects of all other sectors

Given insurance companies provide a wide range on life and non-life policies, they are likely to experience secondary effects of all other sectors suffer due to pandemics

- **Business interruption insurance** – event cancellations
- **Employers liability and workers compensation** – absenteeism from workers who are sick or who do not wish to work and expose themselves, or workers who get sick on the job. Certain sectors are more highly exposed, such as medical workers.
- **Credit insurance** – insurance from company insolvencies
- **Travel insurance** – cancelled business trips and holidays

Pandemic risk exclusions

Another way to mitigate the effects of pandemic risks would be to exclude certain claims in the policy terms. Many insurers for example already exclude war-related claims. Insurance and reinsurers can look to external public bodies such as the World Health Organization to get an independent external assessment of the state of pandemic outbreak (source: Milliman).

Table 20: BofAML covered companies with exposure to the Insurance sector

BBG Ticker	Company	Location	Market Cap (USD)	BofAML Ticker	Pandemics Sector
ACE US	ACE Limited	Bermuda	35,870	ACE	Insurance
AEG US	Aegon	Netherlands	17,357	AEG	Insurance
AFL US	Aflac Inc	United States	26,104	AFL	Insurance
1299 HK	AIA	Hong Kong	64,322	AAIGF	Insurance
AIG US	AIG	United States	95,049	AIG	Insurance
AJG US	AJ Gallagher	United States	6,869	AJG	Insurance
ALL US	Allstate Corp.	United States	33,387	ALL	Insurance
AFG US	Amer Fincl Grp	United States	5,239	AFG	Insurance
AON US	Aon Corporation	United States	29,039	AON	Insurance
ACGL US	Arch Capital	Bermuda	7,380	ACGL	Insurance
AIZ US	Assurant Inc.	United States	4,578	AIZ	Insurance
AV/ LN	Aviva plc	United Kingdom	25,172	AIVAF	Insurance
AXS US	Axis Capital	Bermuda	5,175	AXS	Insurance
2882 TT	Cathay FHC	Taiwan	20,769	CHYYF	Insurance
2823 TT	China Life	Taiwan	2,336	CHLJF	Insurance
CB US	Chubb Corp	United States	22,035	CB	Insurance
CNA US	CNA Financial	United States	10,343	CNA	Insurance
ENH US	Endurance	United States	2,548	ENH	Insurance
HNR1 GR	Hannover Re	Germany	9,874	HVRRF	Insurance
IPCC US	Infinity Ppty	United States	744	IPCC	Insurance
LGEN LN	Legal & General	United Kingdom	23,008	LGGNF	Insurance
LNC US	Lincoln National	United States	14,100	LNC	Insurance
MKL US	Markel Corp.	United States	8,853	MKL	Insurance
MMC US	Marsh & McLennan	United States	27,682	MMC	Insurance
MCY US	Mercury General	United States	2,682	MCY	Insurance
MET US	MetLife Inc.	United States	62,697	MET	Insurance
MUV2 GR	Munich Re	Germany	33,465	MURGF	Insurance
NATL US	Natl Interstate	United States	553	NATL	Insurance
OB US	OneBeacon Insur	United States	1,487	OB	Insurance
PRE US	PartnerRe	United States	5,667	PRE	Insurance

Table 20: BofAML covered companies with exposure to the Insurance sector

BBG Ticker	Company	Location	Market Cap (USD)	BofAML Ticker	Pandemics Sector
1339 HK	PICC GROUP	China	30,911	XFASF	Insurance
2328 HK	PICC P&C	China	18,426	PPCCF	Insurance
2318 HK	Ping An Insura-H	China	69,257	PIAIF	Insurance
PTP US	Platinum	Bermuda	1,665	PTP	Insurance
PFG US	Principal Fincl	United States	15,750	PFG	Insurance
PGR US	Progressive Corp	United States	14,952	PGR	Insurance
PL US	Protective Life	United States	5,411	PL	Insurance
PUK US	Prudential	United Kingdom	59,364	PUK	Insurance
PRU US	Prudential Fincl	United States	41,988	PRU	Insurance
PRU LN	Prudential PLC	United Kingdom	59,364	PUKPF	Insurance
RNR US	RenaissanceRe	Bermuda	3,710	RNR	Insurance
SCR FP	SCOR	France	5,859	SZCRF	Insurance
SIGI US	Selective Ins	United States	1,282	SIGI	Insurance
2888 TT	Shin Kong FHC	Taiwan	2,836	SKFHF	Insurance
SFG US	Stancorp Fincl	United States	2,712	SFG	Insurance
SREN VX	Swiss Re	Switzerland	27,670	XERSF	Insurance
SYA US	Symetra	United States	2,759	SYA	Insurance
HIG US	The Hartford	United States	16,399	HIG	Insurance
TPRE US	Third Point Re	Bermuda	1,602	TPRE	Insurance
TMK US	Torchmark	United States	7,272	TMK	Insurance
TRV US	Travelers Cos	United States	31,042	TRV	Insurance
UNM US	Unum Group	United States	8,680	UNM	Insurance
VR US	Validus Holding	Bermuda	3,682	VR	Insurance
VOYA US	Voya Financial	United States	10,236	VOYA	Insurance
WRB US	W.R. Berkley	United States	6,146	WRB	Insurance
WSH US	Willis Group	United States	7,624	WSH	Insurance
XL US	XL Group	Bermuda	9,222	XL	Insurance

Source: BofA Merrill Lynch Global Research

Travel and Tourism

Non-essential activities that require social contact are likely to suffer the most severe consequences of a pandemic, and unlike previous flu pandemics, international travel and tourism is now a widespread activity that has a tremendous role in the activity and economic livelihood of many countries (source: World Tourism Organization). People would avoid public places such as shopping malls, community centers, places of worship, and transit. General entertainment and leisure activities such as sporting events, museums, and restaurants would decline as well (source: Congressional Budget Office).

Some estimate that in a severe pandemic scenario, demand would plummet 80% for 3 months for entertainment, arts, recreated, lodging, and restaurant industries, and 67% for the transportation sector, including air, rail, and general transit (source: Congressional Budget Office). During the 2003 SARS crisis, it is believed that tourism fell by 90% in the two months in the second quarter of 2003 (source: European Commission). As a result, Asia-Pacific carriers saw revenue plunge $6 billion and North American airlines lost another $1 billion (Source: IATA).

Pandemic impacts through the Travel & Tourism industry will vary greatly from region to region due to their exposure to foreign visitors. In the Caribbean for example, T&T economy accounts for 15.4% of the total economy, and foreign visitors account for a high proportion of all tourism. Conversely, within Europe, foreign visitors account for a small proportion of total, while citizens tend to travel outside of their region for tourism. A pandemic scenario that would restrict people to domestic tourism and spending would actually cushion the economic impact of a pandemic shock (source: WTTC/Oxford Economics).

The role of media and government will have a profound impact on how the public perceives of the severity of the disease and how they behave on the back of it. Media reporting can cause unnecessary panic and cause travel cancellations and changes. Conversely, lack of coverage can create complacency and expose people to unnecessary risks. Various countries and authorities will need to have consistency in their policies given the global nature of a pandemic. They should make a concerted effort to disseminate information, and have consistency in travel restrictions and implementation of basic hygiene rules (source: World Tourism Organization).

Global travel and tourism is now widespread

Unlike the flu pandemics of 1918, 1957 and 1968, international travel and tourism in now a widespread activity that has a tremendous role in the activity and economic livelihood of many countries (source: World Tourism Organization). During the SARS outbreak in 2003, there was a 66% reduction in travel arrivals to Hong Kong. Cinemas in the region experienced a 50% reduction in takings. It is estimated that the Asia Pacific region lost around US$40bn during the outbreak (source: Lloyds).

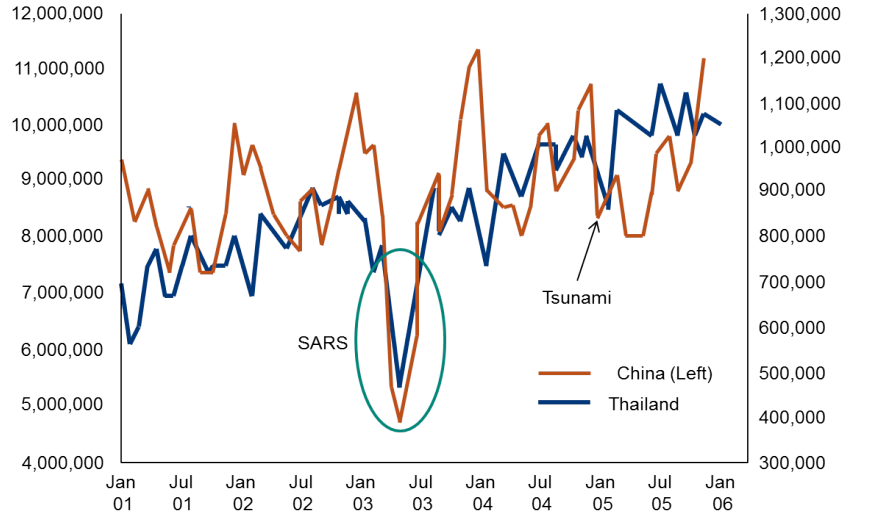
80% drop is CBO's assumption

The US Congressional Budget Office estimates that in a severe pandemic scenario, demand would plummet 80% for 3 months for entertainment, arts, recreated, lodging, and restaurant industries. The transportation sector, including air, rail, and general transit is expected to drop by 67% (source: Congressional Budget Office).

SARS case study, 90% drop in tourism

During the 2003 SARS crisis, which began in southern China and lasted about seven months, business and leisure travellers drastically cut back on flying. While estimates vary, it is believed that tourism fell by 90% in the two months in the second quarter of 2003 (source: European Commission). By April 2003, visitors to Singapore dropped 67% and the country's GDP plummeted by US$950mn (Source: Far Eastern Economic Review). By May 2013, Singapore Airlines had cut capacity by 71% and put its flight staff on unpaid leave (source: Singapore Airlines, Economist).

Chart 21: Initial response to SARS: sudden collapses in tourist arrivals



Source: WHO Pandemic Risk 2014

Significant impact on other sectors

Asia-Pacific carriers saw revenue plunge $6 billion and North American airlines lost another $1 billion (Source: IATA). Average hotel occupancies fell to 20-30% in April 2003 versus 75% in February 2003 (source: Far Eastern Economic Review). Net revenue of Park Place Entertainment, owner of Caesar's Palace in Las Vegas and other gambling and hotel complexes, plunged more than 50% in the second quarter of 2003 compared with the year before, mainly because Asian high rollers cut down on internal travel rather than risk infection, while the war in Iraq contributed to the decline as well (Source: Park Place Entertainment). Retail declined 15% year over year, and restaurant spending dropped sharply as well (source: Congressional Budget Office). However, most studies show that the losses were generally limited to no more than one quarter (source: OECD).

Table 21: Global SARS impacts

Summary of main SARS impacts

	GDP (US$ bn)	Growth	Exports and trade (US$ bn)	Tourism, food and travel (US$ bn)
China	←	↓3% in Q2	↓7.12 (FDI) but 0 (Exports)	↓5 (International) 3.5 (Domestic)
Hong Kong	↓3.7	↓4.75% in Q2	↓23.1 (Outward FDI)	↓0.86 (Tourism) 0.2 (Hotel) 0.26 (Restaurants)
Canada	↓3.2-6.4	↓1% for 2003	↓5.2 (Investment Outflow)	↓0.03 (Tourism) 6.25% (Airline) 4.33 (Accomodation and food)
Singapore	↓4.9	↓1% for 2003	←	↓0.2 (Hotels) 17.4% (Airline)
Malaysia	←	←	←	↓1.7

Table 21: Global SARS impacts

Summary of main SARS impacts

	GDP (US$ bn)	Growth	Exports and trade (US$ bn)	Tourism, food and travel (US$ bn)
Vietnam	←	←	←	↓0.14 (Hotels and restaurants)
Thailand	←	?	←	←33.5 (Tourism)
United States	←	←	←	←
Taiwan	←	←	←	←
Australia	←	←	↓10.1% (2001-2002 decline also)	↓0.119 (Accomodation and food)
Germany	←	←	←	←
Japan	←	?	↓0 Exports but 3.5 (FDI out) and 2.9 (FDI in) but 2001-2002 decline also	←
Mongolia	?	?	←	←
Phillipines	←	?	↓1.2 or 3%	←
France	←	?	←Losses in Q1-3 = Iraq war?	←
Sweden	↓Notable loss, probably not SARS	?	?	←

Source: OECD, KEY: ↓ = SARS related loss, ← = no evidence of a loss, ? = missing

World Travel and Tourism Council study

World Travel and Tourism Council (WTTC) and Oxford Economics completed a joint study on the impact of pandemics on global travel and tourism using two main scenario assumptions – localised, and global. They measure the scope of the Travel & Tourism (T&T) industry in 4 levels by increasing granularity:

- **T&T economy GDP** – The broadest measure, encompassing activity of traditional T&T providers, tourism-related investment, public expending, and export of goods, and the T&T supply chain.
- **T&T direct industry GDP** – Value added of the additional T&T industries excluding indirect effects generated through the supply chain and tourism related investments, public spending, and export of goods.
- **T&T personal consumption** – Travel and tourism spending of residents both domestically and abroad.
- **Visitor Export** – The narrowest measure, considering only the spending on goods and services by international visitors.

Localised case leads to $25.2bn T&T damage

SARS outbreak of 2003 serves as a template for a milder, self-contained scenario of a pandemic, in which geographic impact was limited to only neighbouring countries in a timespan of months. Assuming infection and death rates of 30% and 0.4% respectively, global visitor exports would fall 1% and US$15.1bn loss to travel and tourism (T&T) providers. Moreover, if we figure in the indirect effects of the T&T economy and discouraged investment, that figure rises to US$25.2bn (source: WTTC/Oxford Economics).

Table 22: Impact on T&T economy of localised flu outbreak

	Relative to base	
Year of impact of pandemic	Growth difference % points	Levels in USD bn
Visitor Exports	-1	-10.5
GDP T&T industry (direct)	-0.7	-15.1
GDP T&T economy	-0.4	-25.2

Source: WTTC/Oxford Economics

Global pandemic scenario US$2.5tn in costs

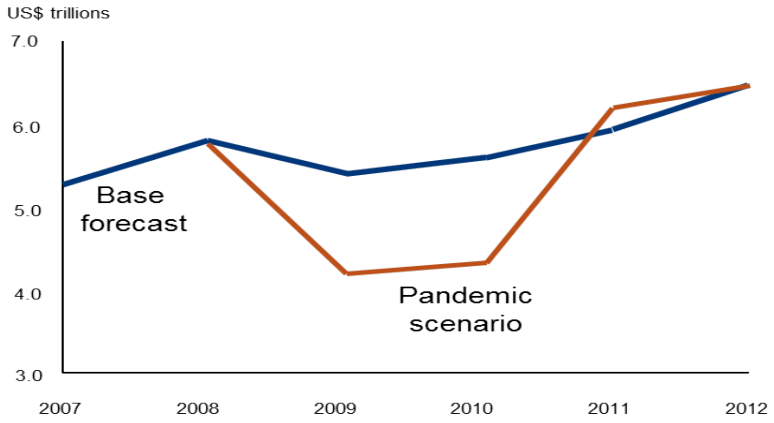
If we take a more extreme scenario in which non-T&T discretionary spending is affect, the economic impact would be exponentially worse. The WTTC study assumed a 30% decline in discretionary spending over a longer 6-month period which also leads to a 10% cut in overall consumption. This would be similar to a global flu scenario. This would cause direct losses to travel & tourism providers of around US$1.07tn and US$2.19 to the global tourism economy, or 3.3% of 2009 GDP. Should the pandemic occur in December around the holiday season, this number would be US$2.5tn (source: WTTC/Oxford Economics).

Table 23: Impact on T&T economy of Global flu outbreak

Year of impact of pandemic	Relative to base: Growth difference % points	Relative to base: Levels in USD bn
Visitor Exports	-59.7	-620
GDP T&T industry (direct)	-53.1	-1073
GDP T&T economy	-36.8	-2190

Source: WTTC/Oxford Economics

Chart 22: Global Travel & Tourism economy GDP scenario under flu pandemic

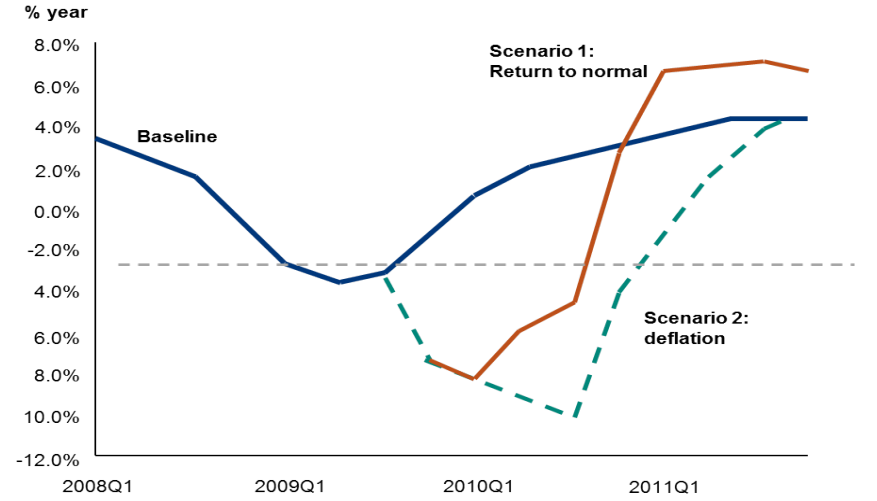


Source: WTTC, Oxford Economics

Pandemic during economic vulnerable time cause deflation

The worst case scenario is if the pandemic hits during global downturns, which could tip the economy into a deflationary environment and prolong downturn instead of allowing for rebound (source: WTTC/Oxford Economics).

Chart 23: World GDP growth



Source: Oxford Economics

Different forms of travel impacted differently

Pandemic risks will vary amongst leisure, business, and family reasons. Leisure travel – international vacations may be oriented more domestically, and there could be higher impact on family vacations. Business travel could be reduced to the necessary minimum. Visits to family and friends would depend on the time of the year because it is normally not considered completely necessary. Moreover, cruise operators may be more heavily impacted because it is perceived as a confined space.

Impact varies by region

Pandemic impacts through the Travel & Tourism industry will vary greatly from region to region due to their exposure to foreign visitors. In the Caribbean for example, T&T economy accounts for 15.4% of the total economy, and foreign

visitors account for a high proportion of all tourism. Conversely, within Europe, foreign visitors account for a small proportion of total, while citizens tend to travel outside of their region for tourism. A pandemic scenario that would restrict people to domestic tourism and spending would actually cushion the economic impact of a pandemic shock (source: WTTC/Oxford Economics).

Table 24: Exposure to shocks to the Travel & Tourism industry by region

Based on 2008 figures	GDP T&T economy as % total	GDP T&T industry direct as % total	Visitor Export as % total	T&T Personal Consumption as % total
Caribbean	15.4	4.7	16.4	6.1
Europe	9.7	3.3	6.1	9.8
North America	9.9	3.6	7.2	8.8
Asia/Oceania	9.5	3.1	4.5	8.8
Africa	9.1	3.3	7.7	5.1
Middle East	10.7	2.7	5.3	10
Latin America	6.8	2.4	4.7	5.5

Source: WTTC/Oxford Economics

All social activities are likely to suffer

Non-essential activities that require social contact are likely to suffer similar declines. People would avoid public places such as shopping malls, community centers, places of worship, and transit. General entertainment and leisure activities such as sporting events, museums, and restaurants would decline. Should we see large-scale school closings, absenteeism is likely to be pronounced as parents stay home to care for their children (source: Congressional Budget Office).

Absenteeism more pronounced in Travel, Tourism, Leisure

Impact of pandemics on the supply side could be more detrimental as well given the labour-intensive nature of the sector (source: World Tourism Organization). The degree of social interaction will be key. Pandemic absenteeism would be especially severe amongst sectors whose products require customers to congregate, such as entertainment, arts, recreation, lodging, and restaurant industries. On the other hand, retail and agriculture sectors would suffer less (source: Congressional Budget Office).

Highly affected by media and fear

The role of media especially at the onset of pandemics can have a profound impact on how the public perceives of the severity of the disease. Media reporting can cause unnecessary panic and cause travel cancellations and changes. Conversely, lack of coverage can create complacency and expose people to unnecessary risks. As we have seen previously, as the virus spreads more widely, people often express less concern over travel, something known as crisis fatigue (source: World Tourism Organization).

Need concerted effort for dissemination of information

Various countries and authorities will need to have consistency in their policies given the global nature of a pandemic. They should make a concerted effort to disseminate information, and have consistency in travel restrictions and implementation of basic hygiene rules (source: World Tourism Organization).

Insurance clauses will have heavy impact

Insurance protection for Travel and Tourism companies would be imperative for the stability of the sector. Certain insurance companies have put in place exclusion causes in cases like pandemics. While this protects insurers against

losses, it removes a pathway by which the Travel & Tourism sector can transfer risk. It would be preferred that insurance companies use reinsurance or capital markets to offload pandemic risk.

Table 25: BofAML covered companies with exposure to the Travel & Tourism sector

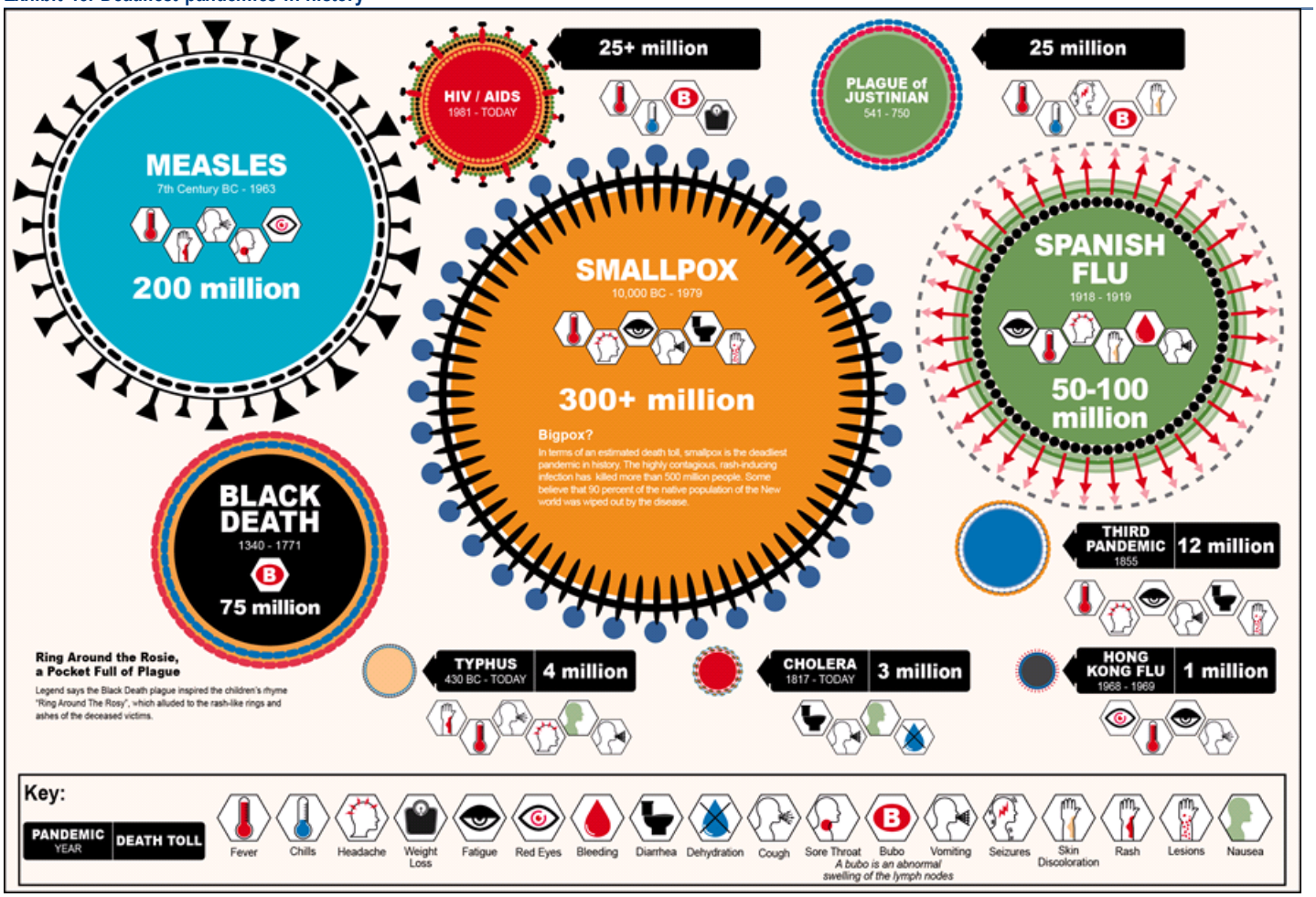
BBG Ticker	Company	Location	Market Cap (USD)	BofAML Ticker	Pandemics Sector
BYD US	Boyd Gaming Corp	United States	1,155	BYD	Travel & Leisure
CZR US	Caesars	United States	1,938	CZR	Travel & Leisure
CCL US	Carnival	United States	31,950	CCL	Travel & Leisure
CCL LN	Carnival	United States	31,133	CUKPF	Travel & Leisure
CVCB3 BZ	CVC	Brazil	857	XTFVF	Travel & Leisure
FLT AU	Flight Centre	Australia	3,874	FGETF	Travel & Leisure
MGM US	MGM Resorts	United States	10,065	MGM	Travel & Leisure
PENN US	Penn Natl Gaming	United States	925	PENN	Travel & Leisure
PNK US	Pinnacle Ent.	United States	1,569	PNK	Travel & Leisure
TCG LN	Thomas Cook	United Kingdom	2,794	TCKGF	Travel & Leisure
AHP US	Ashford Hospitality	United States	520	AHP	Travel & Leisure
CHH US	Choice Hotels	United States	3,084	CHH	Travel & Leisure
DRH US	DiamondRock	United States	2,532	DRH	Travel & Leisure
FCH US	FelCor	United States	1,185	FCH	Travel & Leisure
HCITY* MM	Hoteles City	Mexico	531	HCITY	Travel & Leisure
45 HK	HongkongandShanghai	Hong Kong	2,280	HKSHF	Travel & Leisure
HOT US	Starwood Hotels	United States	16,224	HOT	Travel & Leisure
HST US	Host Hotels	United States	16,225	HST	Travel & Leisure
HT US	Hersha Hospitality	United States	1,348	HT	Travel & Leisure
LHO US	LaSalle	United States	3,546	LHO	Travel & Leisure
LQ US	La Quinta Holdings	United States	2,547	LQ	Travel & Leisure
MAR US	Marriott Intl.	United States	21,952	MAR	Travel & Leisure
MTN US	Vail Resorts	United States	3,072	MTN	Travel & Leisure
PEB US	Pebblebrook	United States	2,438	PEB	Travel & Leisure
RHP US	Ryman	United States	2,430	RHP	Travel & Leisure
RLJ US	RLJ Lodging Trust	United States	3,543	RLJ	Travel & Leisure
69 HK	Shangri-la Asia	Hong Kong	4,760	SHALF	Travel & Leisure
SHO US	Sunstone Hotel Inv	United States	2,505	SHO	Travel & Leisure
9022 JP	JR Central	Japan	28,175	CJPRF	Transport
601006 CH	Daqin Railway	China	19,000	DAQIF	Transport
9020 JP	JR East	Japan	29,812	EJPRF	Transport
525 HK	Guangshen Railway	China	2,833	GNGYF	Transport
9009 JP	Keisei Railway	Japan	3,369	KELRF	Transport
9008 JP	Keio	Japan	4,695	KTERF	Transport
66 HK	MTRC	Hong Kong	23,512	MTRJF	Transport
9007 JP	Odakyu	Japan	6,874	ODERF	Transport
9001 JP	Tobu Railway	Japan	5,645	TBURF	Transport
9005 JP	Tokyu Corp.	Japan	8,436	TOKUF	Transport
9021 JP	JR West	Japan	8,868	WJRYF	Transport
BTSGIF TB	BTSGIF	Thailand	1,769	XYIYF	Transport
FGP LN	FirstGroup Plc	United Kingdom	2,323	FGROF	Transport
GOG LN	Go-Ahead Group	United Kingdom	1,743	GHGUF	Transport
NEX LN	National Express	United Kingdom	2,036	NXPGF	Transport

Source: BofA Merrill Lynch Global Research

Overview of 16 potential pandemics

In this section, we outline a non-exhaustive list of 16 pandemics or infectious diseases that have historically spread through human populations across a large area, or are at potential risk of doing so in the future. For each pandemic, we provide a brief overview including the pathology, symptoms, infection and transmission, historic and current outbreaks and fatalities, economic impacts, and treatment and control.

Exhibit 15: Deadliest pandemics in history



Source: Good, Column Five, Mayo Clinic, CDC, WHO, NCBI, press sources, BofA Merrill Lynch Global Research

Cholera

Cholera is an infection of the small intestine caused by the bacterium Vibrio cholerae.

Symptoms

With a very short incubation period, cholera produces an enterotoxin that causes watery diarrhoea and vomiting. This may result in dehydration and greyish-bluish skin in severe cases. It can lead to death if treatment is not administered in time. Those at very high risk of death have low immunity, such as malnourished children or people with HIV.

Infection and transmission

Transmission occurs primarily by drinking water or eating food that has been contaminated by the faeces (waste product) of an infected person, including one with no apparent symptoms. The bacterium is present in the infected person's faeces for 7-14 days.

Recent outbreaks have been in tandem with the growth of populations living in unsanitary conditions. Cholera is one of the key indicators of a lack of social development, as identified by the World Health Organisation (WHO), and poses a challenge to countries that cannot provide access to safe drinking water and adequate sanitation. Cholera outbreaks or the threat of an epidemic are real risks for almost every developing country.

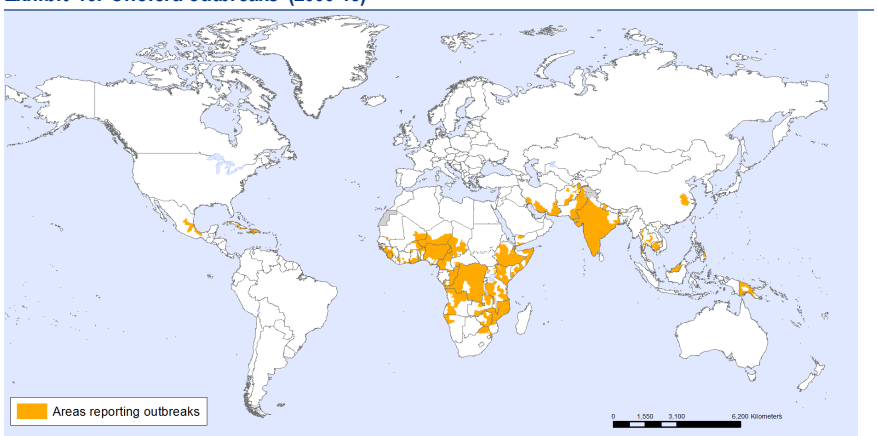
Outbreaks

Cholera started spreading across the world from the reservoir in the Ganges delta in India during the 19th century. Subsequently, there have been six pandemics that have killed millions across the continents. The seventh pandemic (the current one) stated in 1961 in South Asia before reaching Africa in 1971 and finally the Americas in 1991.

Up to 5mn cases every year

Major cholera epidemics affected several regions of the world during 2010-13. In 2011 alone, 589,854 cases were reported from 58 countries that resulted in 7,816 deaths. Many cases go unaccounted due to fear of trade/travel sanctions, and limitations in surveillance systems. However the actual number of cases is estimated to be as high as 3-5mn, causing approx. 100-120,000 deaths annually (source: WHO).

Exhibit 16: Cholera outbreaks (2000-13)



Source: WHO

Economic impact

Cholera outbreaks affect development in the impacted communities and disrupt the social and economic structure of the region. Other countries may restrict travel to the affected regions and curtail imports of certain foods from countries where there is an outbreak. The cholera outbreak in Peru in 1991 had an economic impact of c.US$770mn due to food trade embargoes and affected tourism (source: WHO).

Treatment and control: 80% success rate

Cholera is easily curable and close to 80% of people can be treated successfully through timely oral rehydration to replace water and electrolytes (e.g., a WHO/UNICEF ORS standard sachet). If this is not tolerated or does not provide improvement fast enough, intravenous fluids and appropriate antibiotics are recommended. Antibacterial drugs are beneficial to shorten duration and severity in acute cases. There are currently two effective cholera vaccines; both offer sustained protection of more than 50% that lasts for two years in the case of an endemic.

Ebola

Ebola – or Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF) – is a disease of humans and other primates caused by an ebolavirus.

Symptoms

Ebola is not contagious until symptoms appear. Once a person is infected, the symptoms appear abruptly in 2-21 days. Initially influenza-like symptoms such as headaches, fever, weakness, sore throat and muscle pain can be noticed. Typically, vomiting, diarrhoea and rash follow, along with decreased functioning of the liver and kidneys. This is followed by internal and external bleeding (both within the body and externally). As the early symptoms are very common, it is difficult to diagnose EVD in the initial stages. Five different laboratory tests are required to detect EVD.

Infection and transmission

The virus may be acquired upon contact with blood or bodily fluids of an infected animal. The spread of the disease through the air has not been documented in the natural environment. Fruit bats are believed to be a carrier and may spread the virus without being affected. Once human infection occurs, the disease may spread between people, as well. Male survivors may be able to transmit the disease via semen for nearly two months. To make the diagnosis, other diseases with similar symptoms such as malaria, cholera and other viral hemorrhagic fevers are first excluded. To confirm diagnosis, blood samples are tested for viral antibodies, viral RNA, or the virus itself.

The disease has a high risk of death, killing between 50% and 90% of those infected with the virus.

Table 26: Historic Ebola outbreaks

Year	Country	Cases	Deaths	Case fatality
2012	Dem. Rep. of Congo	57	29	51%
2012	Uganda	7	4	57%
2012	Uganda	24	17	71%
2011	Uganda	1	1	100%
2008	Dem. Rep. of Congo	32	14	44%
2007	Uganda	149	37	25%
2007	Dem. Rep. of Congo	264	187	71%
2005	Congo	12	10	83%
2004	Sudan	17	7	41%
2003 Nov-Dec	Congo	35	29	83%
2003 Jan-Apr	Congo	143	128	90%
2001-2002	Congo	59	44	75%
2001-2002	Gabon	65	53	82%
2000	Uganda	425	224	53%
1996	South Africa (ex-Gabon)	1	1	100%
1996 Jul-Dec	Gabon	60	45	75%
1996 Jan-Apr	Gabon	31	21	68%
1995	Dem. Rep. of Congo	315	254	81%
1994	Cote d'Ivoire	1	0	0%
1994	Gabon	52	31	60%
1979	Sudan	34	22	65%
1977	Dem. Rep. of Congo	1	1	100%
1976	Sudan	284	151	53%
1976	Dem. Rep. of Congo	318	280	88%

Source: WHO

Outbreaks

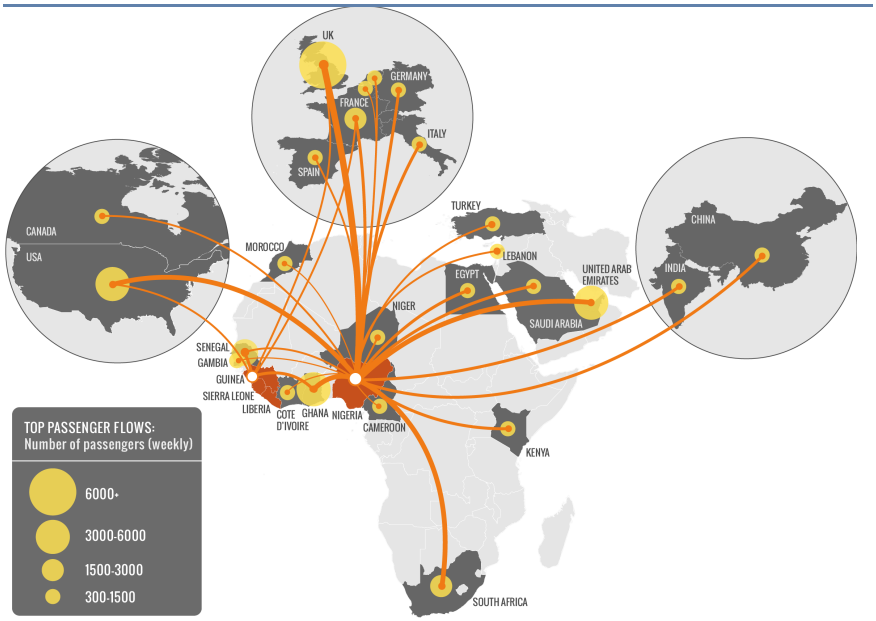
Ebola hemorrhagic fever was first discovered in 1976 near the Ebola River in what is now Sudan and the Democratic Republic of the Congo. The disease typically occurs in outbreaks in tropical regions of sub-Saharan Africa. From 1976 to 2013, the WHO reported a total of 1,716 cases.

2014 outbreak – largest ever, from epidemic to pandemic

The largest outbreak to date is the ongoing 2013-14 West African Ebola pandemic, which is affecting Guinea, Sierra Leone, Liberia and Nigeria. Over half of all documented Ebola cases have occurred in this outbreak. By 6 September 2014, 4,293 suspected cases including 2,296 deaths had been reported, however the WHO has said that these numbers may be vastly underestimated. In September 2014, the CDC estimated that the virus could potentially infect 1.4mn people in Liberia and Sierra Leone by the end of January 2015. The WHO has declared the outbreak to be a Public Health Emergency of International Concern.

A study examining those countries most susceptible to an outbreak showed that Ghana, the United Kingdom, Gambia, the Ivory Coast, and Belgium are most at-risk of importing the disease. Of the 16 countries analysed, the US ranked thirteenth with risk of infection ranging from 1% to 18% (source: PLOS Currents) – with President Obama terming the issue as a "national security priority".

Exhibit 17: It's only a plane ride away – air traffic connections from West Africa to the rest of the world



Source: PLOS

Economic impact

The current Ebola outbreak shows the potential economic impact of pandemics. It has had a huge impact on the global economy apart from the loss of human lives. Tourism has fallen drastically in the West African region. Bookings for hotels and lodgings have decreased significantly. There has been a huge outflow of passenger flight traffic and marginal inflows. Neighbouring countries have halted all trade and transport to and from other affected countries. In Sierra Leone, local banks, markets, educational institutes and shops have been shut.

The GDP growth rates of affected countries have also been affected. The World Bank revised down the economic growth rate estimate of Guinea by 100bp. The Liberian finance minister also declared the IMF's 5.9% growth projection as unrealistic. Governmental expenditures on medical services will significantly impact the growth rate of affected African countries.

Treatment

There is no specific vaccine or treatment available for Ebola. Treatment is limited to supportive therapy, which includes maintaining blood pressure, consistent oxygen support, balancing body fluids and preventing dehydration via oral rehydration, managing bleeding, and treating bacterial infections through the administration of available drugs. Other measures include: blood products, regulators of coagulation, and medication for malaria and bacterial infections. Early treatment may increase the chance of survival.

Containment is key

Ebola poses a huge biohazard risk and infected people or populations need to be quarantined immediately. Typically, doctors and nurses segregate infected patients, and use and dispose of protective clothing and objects effectively. While successfully treated patients become immune to the virus, it can be spread through semen up to seven weeks after clinical recovery. Contact tracing and safe burials continue to be of concern in light of the increasing number of cases and deaths. Of particular concern is the safety of community burials and mass cremation.

Prevention is key

Prevention includes decreasing the spread of disease from infected animals to humans. This may be done by checking animals for infection and killing and disposing of the carcasses properly if the disease is discovered. Properly cooking meat and wearing protective clothing when handling meat may also be helpful, as is wearing protective clothing and washing hands when around a person with the disease. Samples of bodily fluids and tissues from those infected with the disease need to be handled with special caution.

Treatments under development

A number of experimental treatments including vaccines are being studied. The US FDA has allowed two drugs, ZMapp and an RNA interference drug called TKM-Ebola, to be used in people infected with Ebola during the 2014 outbreak. FujiFilm, Tekmira and Protalix also have potential treatments.

Hendra and Nipah

Hendra virus (HeV)

HeV infection is an emerging zoonosis that causes severe diseases in humans and horses. Fruit bats of the Pteropodidae family have been identified as the natural hosts of the virus. The virus was first identified in Australia (Hendra) in 1994 during an outbreak that involved 21 horses and a couple of cases in humans. Up until July 2008, 11 outbreaks of the virus have been reported – all restricted to east coast of Australia.

Horses are the intermediate hosts responsible for transmitting infection to humans through close contact during the care of ill or dead horses. The symptoms of the virus in infected humans range from a mild influenza-like illness to fatal respiratory or neurological disease.

No vaccine is available for humans or animals; the primary treatment for humans is intensive supportive care. Horses are the only animals with a reported natural infection of HeV with fatality at approximately 75%.

Nipah virus (NiV)

NiV occurs in both humans and animals and is an emerging zoonosis infection. Fruit bats belonging to the Pteropodidae family carry the NiV, which was first identified in Malaysia (Nipah) in 1998. During this outbreak, pigs were the intermediate hosts; however, in subsequent ones, there were no intermediate hosts. Human-to-human transmission has also been documented for this virus.

NiV infection in humans causes asymptomatic infection, leading to acute respiratory syndrome and fatal encephalitis.

Currently, no vaccine is available and the primary treatment is intensive support care.

HIV/AIDS

Human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV).

Symptoms

The term HIV/AIDS represents the entire range of diseases caused by the human immunodeficiency virus from early infection to late stage symptoms. During the initial infection, a person may experience a brief period of influenza-like illness (fever, headache, rash or sore throat). This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more with the immune system, making the person much more susceptible to infections, including opportunistic infections and tumours that do not usually affect people with working immune systems. The primary causes of death from HIV/AIDS are opportunistic infections and cancer, both of which are frequently the result of the progressive failure of the immune system.

Transmission and infection

HIV (Human Immunodeficiency Virus) attacks the immune cells, thereby increasing susceptibility to a wide range of infections that would normally not affect a healthy person easily. AIDS (Acquired Immunodeficiency Syndrome) is the most advanced stage of the HIV infection.

Table 27: Global AIDS epidemic

Number of people living with HIV in 2013	Total	35.0 mn [33.1 mn – 37.2 mn]
	Adults	31.8 mn [30.1 mn – 33.7 mn]
	Women	16.0 mn [15.2 mn – 16.9 mn]
	Children (<15 years)	3.2 mn [209 mn – 3.5 mn]
People newly infected with HIV in 2013	Total	2.1 mn [1.9 mn – 2.4 mn]
	Adults	1.9 mn [1.7 mn – 2.1 mn]
	Children (<15 years)	240 000 [210 000 – 280 000]
AIDS deaths in 2013	Total	1.5 mn [1.4 mn – 1.7 mn]
	Adults	1.3 mn [1.2 mn – 1.5 mn]
	Children (<15 years)	190 000 [170 000 – 220 000]

Source: WHO

HIV is transmitted primarily via unprotected sexual intercourse (including anal and oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Individuals cannot become infected through ordinary day-to-day contact such as kissing, hugging, shaking hands, or sharing personal objects, food or water. The majority of transmissions worldwide occur through heterosexual contacts; however, the pattern of transmission varies significantly among countries. The most dangerous phase is immediately after infection when a person may not realise that they are infected. Major risk factors are unprotected sex with multiple partners and sharing contaminated needles.

HIV is diagnosed by identifying the presence of HIV antibodies in the blood during the laboratory test. The immune system is responsible for generating antibodies to fight foreign pathogens in the body. HIV antibodies are produced for a period of 3-6 weeks before being detected after the person is infected. The infectivity is highest during the early period of infection; however, the transmission could occur at any stage.

Outbreaks

Genetic research indicates that HIV originated in west-central Africa during the late nineteenth or early twentieth century. AIDS was first recognised by the CDC in 1981 and its cause, HIV infection, was identified in the early part of the decade.

Since its emergence, HIV has become the most significant pathogen in the world, claiming the lives of over 39mn people. At the end of 2013, there were approximately 35mn people living with the disease and 2.1mn reported new cases globally, which is down from 3.1mn new infections in 2001 (source: WHO). It resulted in about 1.6mn deaths in 2012, down from a peak of 2.2mn in 2005 (source: UN). HIV/AIDS is considered a global pandemic – i.e., a disease outbreak which is present over a large area and is spreading actively.

Sub-Saharan Africa is the most affected region. In 2010, an estimated 68% (22.9mn) of all HIV cases and 66% of all deaths (1.2mn) occurred in this region (source: WHO, UN). This means that about 5% of the adult population is infected. South Africa has the largest population of people with HIV in the world at 5.9mn. South and Southeast Asia are the next most affected regions, with an estimated 4mn cases in 2010 or 12% of all people living with HIV, resulting in approximately 250,000 deaths. Approximately 2.4mn of these cases are in India (source: UN). In 2008, in the US, approximately 1.2mn people were living with HIV, resulting in about 17,500 deaths: with an estimated 20% unaware of their infection (source: CDC).

Economic impact

According to the UN, HIV/AIDS can slow the rate of GNP of the impacted countries by 1% for every 10% HIV prevalence. It can decelerate the growth in labour markets. Health expenditures take their toll on family savings and investments, and could impact children's education, health and nutrition. HIV/AIDS also results in the potential diversion of public spending from physical and human capital to health expenditure. It could also derail foreign and domestic private investment if the epidemic spreads.

Treatment

Although the virus cannot be cured it can be kept at bay with proper medication. It may take 2-15 years to develop AIDS but not everyone who is infected will progress to the final stage. An early diagnosis coupled with proper treatment can

lead to a nearly normal life expectancy. Without treatment, the average survival time after infection with HIV is estimated at 9-11 years, depending on the HIV subtype.

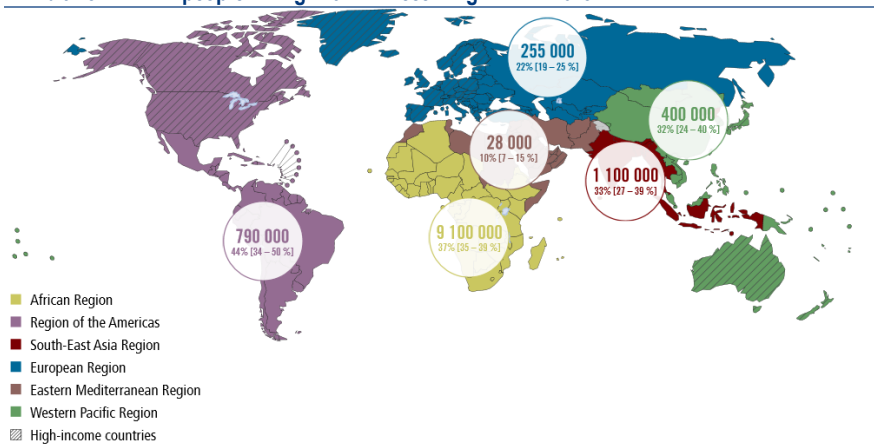
There is no cure or vaccine; however, antiretroviral therapy (ART) can slow the course of the disease and may lead to a near-normal life expectancy. Antiretroviral therapy (ART) along with a combination of 3+ ARV drugs is used to suppress HIV. ART can only control the replication of virus in the body but does not have the ability to cure it. It only helps in strengthening the infected individual's immune system to regain the capacity to fight off infections. Approximately 11.7mn people including 740,000 children in low- to middle-income countries received ART treatment in 2013. Only 38% of adults infected with HIV were receiving treatment and just 24% of infected children (source: UN).

There is evidence that a vaccine may be possible. Work with monoclonal antibodies (MAb) has shown or proven that the human body can defend itself against HIV, and certain individuals remain asymptomatic for decades after HIV infection. Potential candidates for antibodies and early stage results from clinical trials have been announced. A single trial of the vaccine RV 144 published in 2009 found a partial reduction in the risk of transmission of roughly 30%, stimulating some hope in the research community of developing a truly effective vaccine. Further trials of the RV 144 vaccine are ongoing.

Prevention is key

Prevention of HIV infection, primarily through safe sex and needle-exchange programmes, is a key strategy to control the spread of the disease. The use of condoms is highly effective along with limiting the number of sex partners. Regular testing for anyone who is exposed to the major risk factors is strongly advised and taking a daily pill of pre-exposure prophylaxis can also lower the risk of infection.

Exhibit 18: 11.7mn people living with HIV receiving ART in 2013



Source: WHO

Influenza

Influenza (or flu) is an infectious disease of birds and mammals caused by RNA viruses of the Orthomyxoviridae family.

Virology

In virus classification, influenza viruses are RNA viruses that make up three of the five genera of the Orthomyxoviridae family:

- **Influenza A**: Wild aquatic birds are the natural hosts for a large variety of influenza A. Occasionally viruses are transmitted to other species and may then cause devastating outbreaks in domestic poultry or give rise to human influenza pandemics. The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. Serotypes that have been confirmed in humans include H1N1 (Spanish Flu in 1918, and Swine Flu in 2009); H2N2 (Asian Flu in 1957); H3N2 (Hong Kong Flu in 1968); and H5N1 (Bird Flu in 2004).

- **Influenza B**: Influenza B almost exclusively infects humans and is less common than influenza A. Q degree of immunity to influenza B is usually acquired at an early age.

- **Influenza C**: This virus infects humans, dogs and pigs, sometimes causing both severe illness and local epidemics. it is less common than the other types and usually causes only mild disease in children.

Symptoms

The most common symptoms appear after one to two days of infection and include chills, fever, runny nose, sore throat, muscle pains, headache (often severe), coughing, weakness/fatigue and general discomfort. Although it is often confused with other influenza-like illnesses, especially the common cold, influenza is a more severe disease. Influenza may produce nausea and vomiting, particularly in children, but these symptoms are more common in the unrelated gastroenteritis, which is sometimes inaccurately referred to as "stomach flu" or "24-hour flu".

It can be difficult to distinguish between the common cold and influenza in the early stages of these infections, but flu can be identified by a high fever with a sudden onset and extreme fatigue. Influenza is a mixture of symptoms of common cold and pneumonia, body ache, headache and fatigue.

Flu can occasionally lead to pneumonia, either direct viral pneumonia or secondary bacterial pneumonia, even in healthy persons.

Infection and transmission

Influenza can be spread by direct transmission (when an infected person sneezes mucus directly into the eyes, nose or mouth of another person); airborne route (when someone inhales the aerosols produced by an infected person coughing, sneezing or spitting): and through hand-to-eye, hand-to-nose, or hand-to-mouth transmission, either from contaminated surfaces or from direct personal contact such as a handshake (as the virus can exist outside of the body). Airborne aerosols have been thought to cause most infections, although it is not absolutely clear which means of transmission is most important.

Influenza virus shedding (the period when a person might be infectious to another person) begins the day before symptoms appear and the virus is then released

for five to seven days. People who contract influenza are most infective between the second and third day after infection. The amount of virus shed appears to correlate with fever, with higher amounts of virus shed when temperatures are highest. Children are much more infectious than adults and shed virus from just before they develop symptoms until two weeks after infection.

Outbreaks

The symptoms of human influenza are noted dating back to the ancient Greek with the first convincing record of an influenza pandemic taking place in the 1500s and then continuing sporadically throughout the 17-19th centuries. The most lethal outbreak was the 1918 Spanish flu pandemic (type A influenza, H1N1 subtype), which lasted from 1918 to 1919 and is thought to have killed 50-100mn people. The death toll was caused by an extremely high infection rate of up to 50% and the severity of the symptoms, suspected to be caused by cytokine storms. The 1918 pandemic was global and killed between 2% and 20% of those infected. Later flu pandemics include the 1957 Asian Flu (type A, H2N2 strain) and the 1968 Hong Kong Flu (type A, H3N2 strain), which killed millions of people.

Influenza spreads around the world in seasonal epidemics, resulting in c.3-5mn cases of severe illness pa and about 250,000 to 500,000 deaths ever year, rising to millions in some pandemic years. In the 20th century, three influenza pandemics occurred; each was caused by the appearance of a new strain of the virus in humans and killed tens of millions of people.

Often, new influenza strains appear when an existing flu virus spreads to humans from another animal species, or when an existing human strain picks up new genes from a virus that usually infects birds or pigs. An avian strain named H5N1 raised the concern of a new influenza pandemic after it emerged in Asia in the 1990s, but it has not evolved to a form that spreads easily between people. In April 2009, a novel flu strain evolved that combined genes from human, pig and bird flu. Initially dubbed "swine flu" and also known as influenza A/H1N1, it emerged in Mexico, the US and several other nations. The WHO officially declared the outbreak to be a pandemic in June 2009.

Table 28: Major influenza epidemics

Name of pandemic	Date	Deaths	Case fatality rate	Subtype involved	Pandemic Severity Index
1889–1890 flu pandemic (Asiatic or Russian Flu)	1889–1890	1 million	0.0015	possibly H3N8 or H2N2	NA
1918 flu pandemic (Spanish flu)	1918–1920	20 to 100 million	0.02	H1N1	5
Asian Flu	1957–1958	1 to 1.5 million	0.0013	H2N2	2
Hong Kong Flu	1968–1969	0.75 to 1 million	<0.1%	H3N2	2
Russian flu	1977–1978	no accurate count	N/A	H1N1	N/A
2009 flu pandemic	2009–2010	105,700-395,600	0.0003	H1N1	NA

Source: WHO, CDC, Mayo Clinic, BofA Merrill Lynch Global Research

Economic impact of H7N9 China outbreak at US$6.5bn

A study (source: Qi and Gao, 2014) estimates that the Chinese poultry industry suffered direct losses of US$1.24bn in affected provinces and US$0.59bn in unaffected regions. The government spent around US$97mn on the development of the poultry industry. UN experts estimated that the Chinese economy suffered

an overall loss of around US$6.5bn, due largely to bird market restrictions. Along the same lines, the Chinese agriculture ministry estimated a US$6.5bn loss in the agriculture sector due to the collapse in prices, consumer confidence and trade.

Treatment

People with the flu are advised to get plenty of rest, drink lots of liquids, avoid alcohol and tobacco and, if necessary, take medications such as acetaminophen (paracetamol) to relieve the fever and muscle aches associated with the flu. Since influenza is caused by a virus, antibiotics have no effect, unless prescribed for secondary infections such as bacterial pneumonia.

Antiviral medication may be effective, but some strains of influenza can show resistance to the standard antiviral drugs and there is concern about the quality of the research. The two classes of antiviral drugs used against influenza are neuraminidase inhibitors (oseltamivir and zanamivir) and M2 protein inhibitors (adamantane derivatives).

Vaccinations against influenza are recommended for high-risk groups (children, the elderly, healthcare workers, and people who have chronic illnesses such as asthma, diabetes, heart disease, or are immuno-compromised). In healthy adults, it is modestly effective in decreasing the amount of influenza-like symptoms in a population. A particular influenza vaccine usually confers protection for no more than a few years, due to the high mutation rate of the virus. As a result, every year, the WHO predicts which virus strains are most likely to be circulating the next year, allowing pharmaceutical companies to develop vaccines that will provide the best immunity against these strains.

Farmed poultry is often vaccinated to avoid devastation of the flocks. The most common human vaccine is the trivalent influenza vaccine (TIV) that contains purified and inactivated antigens from three viral strains. Typically, this vaccine includes material from two influenza A virus subtypes and one influenza B virus strain. The TIV carries no risk of transmitting the disease. A vaccine formulated for one year may be ineffective the following year, since the influenza virus evolves rapidly, and new strains quickly replace the older ones.

Prevention is key

Reasonably effective ways to reduce the transmission of influenza include good personal health and hygiene habits. Since influenza spreads through both aerosols and contact with contaminated surfaces, influenza viruses can be inactivated by sunlight, disinfectants and detergents. As the virus can be inactivated by soap, frequent hand washing reduces the risk of infection. Face masks might help prevent transmission when caring for the sick,

During past pandemics, closing public places such as schools, churches and theatres slowed the spread of the virus but did not have a large effect on the overall death rate.

Malaria

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a type of single cell microorganism) of the Plasmodium type.

Symptoms

Malaria causes symptoms that typically include fever, fatigue, vomiting and headaches. In severe cases it can cause yellow skin, seizures, coma or death.

These symptoms usually begin 10 to 15 days after being bitten. In those who have not been appropriately treated, the disease may recur months later. In those who have recently survived an infection, re-infection typically causes milder symptoms. This partial resistance disappears over months to years, if there is no ongoing exposure to malaria. The first symptoms may be mild and difficult to recognise. If not treated within 24 hours, falciparum malaria can progress to severe illness often leading to death (as malaria impacts the blood supply to vital organs).

Infection and transmission

Commonly, the disease is transmitted to humans and animals by the bite of an infected female Anopheles mosquito. This bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites then travel to the liver where they mature and reproduce. Five species of Plasmodium can infect and be spread by humans. Most deaths are caused by P. falciparum. P. vivax, P. ovale, and P. malariae generally cause a milder form of malaria. The species P. knowlesi rarely causes disease in humans.

Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests. Methods that use the polymerase chain reaction to detect the parasite's DNA have been developed, but are not widely used in areas where malaria is common due to their cost and complexity.

Outbreaks

The parasite responsible for malaria has been in existence for 50-60,000 years and there are references to periodic fevers of malaria throughout recorded history, beginning in 2700 BC in China. Close to half of the world's population (approx. 3.4bn people) are currently at risk of malaria according to the WHO. The disease is widespread in tropical and subtropical regions, which are present in a broad band around the equator. This includes much of Sub-Saharan Africa, Asia, and Latin America. In 2012, the WHO estimated 207mn cases of malaria and between 473,000 and 789,000 death in the same year, many of which were children in Africa.

In 2013, 97 countries and territories had ongoing malaria transmission. However, the global mortality rates due to malaria have fallen by 42% since 2000 and by 49% in Africa (source: WHO).

Climate change is likely to affect malaria transmission, in our view, but the severity and geographic distribution of such effects is currently uncertain.

Table 29: Reported malaria cases by region ('000)

Cases	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific	World
2000	173,600	2,240	15,960	40	31,380	2,930	226,100
2001	178,000	1,754	15,570	28	30,970	2,537	228,800
2002	182,100	1,606	15,830	24	28,740	2,266	230,500
2003	186,600	1,552	15,610	19	29,750	2,496	236,000
2004	189,700	1,535	14,830	11	30,750	2,774	239,600
2005	192,400	1,685	13,340	6	34,300	2,283	244,000
2006	189,800	1,430	13,760	3	28,680	2,405	236,100
2007	185,200	1,230	12,980	1	26,150	1,877	227,400
2008	181,000	941	12,800	0.7	28,550	1,722	225,100
2009	175,700	1,000	11,580	0.34	28,700	2,111	219,100

Table 29: Reported malaria cases by region ('000)

Cases	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific	World
2010	170,100	1,065	12,480	0.21	28,240	1,668	213,500
2011	165,500	846	12,670	0.09	25,420	1,406	205,800
2012	165,200	790	13,240	0.03	26,790	1,410	207,400

Source: WHO

Economic impact

Malaria is commonly associated with poverty and has a major negative effect on economic development. In Africa, it is estimated to result in direct losses of US$12bn a year due to increased healthcare costs, the lost ability to work and effects on tourism (source: Greenwood et al, The Lancet). The cost in lost economic growth is many times more than that. (Source: CDC) Taking into account initial poverty, economic policy, tropical location, and life expectancy, among other factors, countries with intensive malaria grew 1.3% less per person per year, and a 10% reduction in malaria was associated with 0.3% higher growth. (Source: Gallop and Sachs, The Economic Burden of Malaria).

Treatment

Early diagnosis and treatment prevent deaths and contribute to reducing transmission. The recommended treatment is a combination of antimalarial medications that include an artemisinin-based combination therapy (ACT), which decreases resistance to any single drug component. The second medication may be either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine. Quinine along with doxycycline may be used if an artemisinin is not available. Several medications are available to prevent malaria in travellers to areas where the disease is common.

Occasional doses of the medication sulfadoxine/pyrimethamine are recommended in infants and after the first trimester of pregnancy in areas with high rates of malaria.

No vaccine exists

Despite a need, no effective vaccine exists, although efforts to develop one are ongoing. GSK has developed a vaccine called RTS,S (Mosquirix) with the potential to reduce the number of cases in children by 50%. This vaccine has finished clinical trials and the results will be submitted to the WHO for approval, which is expected to be granted in early 2015. The company aims to sell it at not-for-profit price, keeping a mere 5% margin on sales.

Table 30: Major companies manufacturing malaria drugs

Generic Name	Trade Name	Company	Country
Atovaquone\proguanil hydrochloride	Malarone	GlaxoSmithKlien	England
Chloroquine Phosphate	Aralen	Sanofi Aventis US	US
Doxycycline	Vibramycin	Pfizer Inc.	US
	Monodox	Aqua Pharms	Us
Mefloquine	Lariam	Hoffmann–La Roche	Switzerland
	Mephaquin	Mepha Ltd	Switzerland
	Mefliam	Cipla Ltd	India
Primaquine phosphate	Primaquine	Sanofi Aventis US	US
	Primaquine phosphate	Bayshore Pharms LLC.	US

Source: FDA

US$5.1bn pa required till 2020

Total spending on malaria control in 2011 was estimated to be US$2.3bn. The global requirements for the fight against malaria are anticipated to exceed US$5.1bn per year between 2011 and 2020, highlighting a funding gap of US$2.8bn (source: WHO).

Increasing drug resistance

Resistance to several antimalarial medications has developed; for example, chloroquine-resistant P. falciparum has spread to most malarial areas, and resistance to artemisinin has become a problem in some parts of Southeast Asia (Burma, Cambodia, Laos, Thailand and Vietnam).

Prevention is key

The risk of disease can be reduced by preventing mosquito bites by using mosquito nets and insect repellents, or mosquito-control measures such as spraying insecticides and draining standing water.

Measles

Measles – also known as morbilli, English measles, and rubeola – is an infection of the respiratory system, immune system and skin caused by a virus, specifically a paramyxovirus of the genus Morbillivirus.

Table 31: Measles facts

Year	Fact
2015	MDV to reduce child mortality by 2/3
2012	122,000 fatalities due to measles
2000-2012	78% drop in fatalities due to vaccination
2000-2012	1 billion vaccinated
2012	145 million vaccinated

Source: WHO

Symptoms

Common symptoms include fever, runny nose, cough, rash, conjunctivitis and Koplik's spots (inside the mouth). Fever is the first sign starting a few days after infection. The rash generally starts a couple of weeks after infection and begins from the hairline working its way down, while this coincides with a hike in fever. It is common for the rash to subside after 5-6 days. The course of measles, provided there are no complications, such as bacterial infections, usually lasts about 7-10 days. Complications are possible in children under five and adults over 20; these include blindness, encephalitis, severe diarrhoea, dehydration, ear infections and pneumonia.

Infection and transmission

Measles is spread through respiration (e.g., coughing and sneezing or contact with nasal or throat secretions). It is also spread through direct hand contact with infected surfaces if the hand is subsequently brought in contact with the mouth or nose. It is highly contagious – 90% of people without immunity sharing living space with an infected person will catch it. This is because air or an infected surface can be a contagious medium for up to two hours. Infection may be passed on up to four days before or four days after the appearance of the characteristic rash.

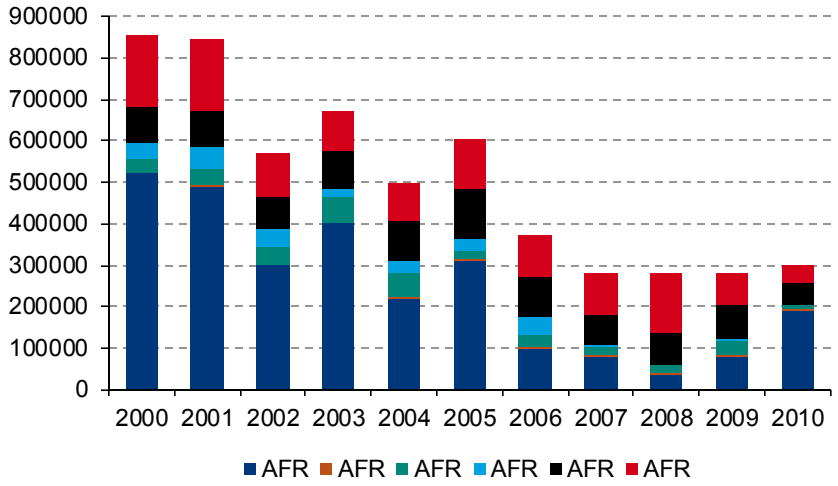
Outbreaks

Measles is one of the most infectious diseases to affect humans. Between the mid-1800s and early 2000s, measles is estimated to have killed about 200mn people worldwide. Before the advent of a suitable vaccination, over 90% of children below the age of 15 were infected. Today, secondary attach rates are still 90% of those susceptible. One must be either unvaccinated or not have had the disease previously to be susceptible.

There are still 20mn cases annually and in 2008 there were 164,000 deaths worldwide, of which 77% occurred in Southeast Asia (source: WHO). Thanks to vaccination, there are 14mn fewer child fatalities today than in 2000. Measles

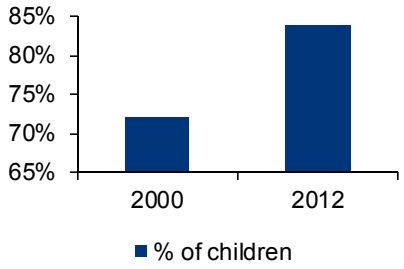
vaccination coverage is an indicator of the fourth Millennium Development Goal, which aims to reduce the under-five mortality rate by two-thirds by 2015.

Chart 24: Number of reported measles cases (2000-2010)



Source: WHO

Chart 25: % of world's children vaccinated



Source: WHO

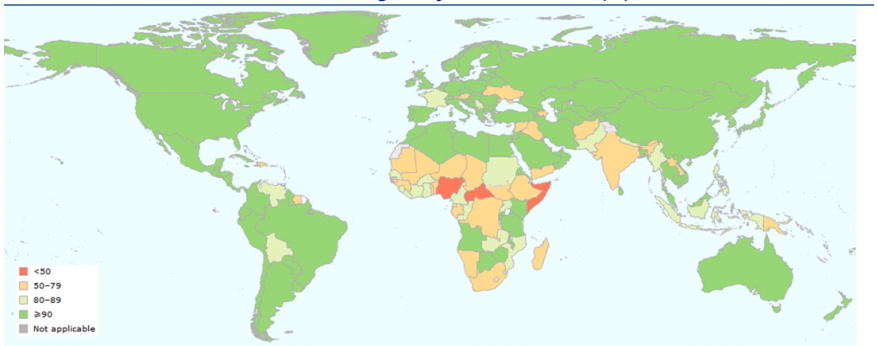
Treatment & control

There is no specific treatment for measles. The immune system needs to overcome the disease on its own. This is aided by resting in low-light conditions and the intake of adequate fluid to prevent dehydration. It generally takes 7-10 days to recover. Children in developing countries are given two doses of Vitamin A, which helps prevent eye damage and blindness. Vitamin A supplements also reduce the fatality rate by 50%. After recovery a person will become immune to the virus.

The MMR (measles-mumps-rubella-varicella) vaccine is administered to 84% of the world's children before their first birthday. Two doses are recommended as 15% of vaccinated children fail to develop immunity after their first dose. All 194 WHO Member States are committed to reduce measles deaths by 95% by 2015.

As measles grows in the cells that line the back of the throat and lungs, it is a uniquely human disease. This means there are no known animal reservoirs and complete eradication is possible.

Exhibit 19: Measles immunisation among one year olds in 2012 (%)



Source: WHO

Meningitis

Meningitis is an acute inflammation of the membrane (meninges) covering the brain and spinal cord that is usually caused by a bacterial or viral infection of the cerebrospinal fluid.

Symptoms

Symptoms are similar for both bacterial and viral meningitis and include fever, nausea, vomiting, neck stiffening, increased sensitivity to light (photophobia) and loud noises, and confusion. Children often exhibit only nonspecific symptoms, such as irritability and drowsiness. The later symptoms of bacterial meningitis can be severe and result in seizures and coma. Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord; therefore, the condition is classified as a medical emergency. Meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus and cognitive deficits, especially if not treated quickly.

Infection and transmission

Meningitis is typically caused by an infection with microorganisms – typically due to viruses, with bacteria, fungi, and protozoa being the next most common causes. It may also result from various non-infectious causes. The term aseptic meningitis refers to cases of meningitis in which no bacterial infection can be found. Meningitis may be encountered in cerebral malaria (malaria infecting the brain) or amoebic meningitis, meningitis due to infection with amoebae contracted from freshwater sources.

Bacteria can be spread through the exchange of respiratory and throat secretions. These bacterial are not as contagious as the common flu viruses. The disease is not airborne and casual contact with an infected person is not harmful. Viral meningitis is spread through respiratory droplets and faecal matter. Other viral diseases like the mumps, measles and influenza can also lead to viral meningitis.

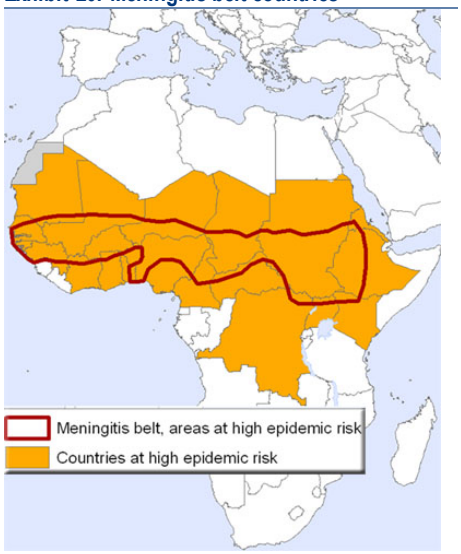
Viral meningitis is more common than bacterial but less severe. Most patients recover fully and there is no specific treatment required. The elderly and people suffering from immunity disorders are more at risk.

Table 32: Meningococcal outbreaks outside Africa

Year	Country
May-2005	India
Jan-2005	Philippines
May-2000	Singapore, Indonesia, Iran and Morocco
Apr-2000	the United States
Apr-2000	France and UK
Jan-1999	Hungary

Source: WHO

Exhibit 20: Meningitis belt countries



Source: CDC

Outbreaks

It appears that epidemic meningitis is a relatively recent phenomenon dating back to the 1800s. The first report of an epidemic in Africa appeared in 1840 and African epidemics became much more common in the 20th century. Since 1988, there have been over 1mn cases of meningitis reported in Africa. Major epidemic cycles are detected every 8-12 years and the cycle period appears to be growing shorter. The main causative agent in 80-85% of all cases has been meningococcal. Geographically, epidemics are concentrated in the sub-Saharan region, from Senegal in the west to Ethiopia in the east. Meningococcal disease (Neisseria meningitidis) is the leading cause of meningitis in the meningitis belt. At any given time, 10-25% of the global population carries meningococcal bacteria in the back of their throats or in their noses. There is a seasonality associated with the outbreaks which usually occur in the dry season, last for 2-3 years and then die out in the rainy season.

Bacterial meningitis ranks high in terms of severity as it can result in permanent disability or death within hours. Fatality rates are as high as 50% if left untreated and worldwide there are 170,000 deaths reported each year. Children under one are the most prone to this disease although it can affect any age group.

Treatment

Bacterial meningitis can be treated with antibiotics and there is a recommended vaccination schedule for prevention. No vaccines are available for viral meningitis and antibiotics are ineffective; most patients recover on their own.

The first treatment in acute meningitis consists of promptly administered antibiotics and sometimes antiviral drugs. Corticosteroids can also be used to prevent complications from excessive inflammation. Some forms of meningitis (such as those associated with meningococci, Haemophilus influenzae type B, pneumococci or mumps virus infections) may be prevented by immunisation.

The introduction of an affordable meningococcal A conjugate vaccine called MenAfriVac is expected to save nearly 150,000 lives by 2015 and free up US$120mn in government funding.

Methicillin-resistant staphylococcus aureus (MRSA)

Methicillin-resistant staphylococcus aureus (MRSA) – or oxacillin-resistant Staphylococcus aureus (ORSA) is a strain of Staphylococcus aureus (S-aureus, commonly called "staph") bacteria that is resistant to many antibiotics and is responsible for several difficult-to-treat infections in humans.

Symptoms

MRSA mostly appears as a skin infection that starts as small red bumps resembling pimples, boils or spider bites. Pus or other fluids may drain from this area. These can turn into deep abscesses if the skin has been cut or rubbed. MRSA infection at healthcare facilities can be severe, affecting the bloodstream, heart, lungs, urine or the area of a recent surgery. These may cause chest pain, cough or shortness of breath, fatigue, chills, fever, general ill feeling, headaches, rash or wounds that do not heal.

Table 33: MRSA is resistant to following antibiotics

Drug name	Still effective for
Penicillin	Ear Infection
Methicillin	Certain Staph Infections
Nafcillin	Bacterial Blood Infection
Oxacillin	Bacterial Blood Infection
Amoxicillin	Strep throat
Clindamycin	Urinary Tract infection
Vancomyin	Bacterial Intestine Infection

Source: BofAML Global Research

Infection and transmission

MRSA is especially troublesome in hospitals, prisons, and nursing homes, where patients with open wounds, invasive devices, and weakened immune systems are at greater risk of nosocomial infection than the general public. Although MRSA began as a hospital-acquired infection, it has developed limited endemic status and is now sometimes community-acquired. MRSA is thus categorised according to where the infection was acquired: hospital-acquired (HA-MRSA) or community-associated (CA-MRSA).

In a hospital, HA-MRSA can spread on the hands of doctors, nurses, other healthcare providers or visitors. It can also spread on contaminated objects, such as bed linens, bed rails, bathroom fixtures, and medical equipment. Community-associated MRSA (CA-MRSA) spreads in crowded settings through: 1) close skin-to-skin contact; 2) sharing of personal items such as towels, razors, and sporting equipment; and 3) compromise in personal hygiene.

Outbreaks

S-aureus bacterium, commonly known as staph, was discovered in the 1880s. In the 1940s, treatment for S-aureus infections became routine with the discovery of antibiotic medicine, such as penicillin. However, by the late 1950s, 50% of all S-aureus were resistant to penicillin. Some strains of S-aureus evolved resistance to methicillin and cephalosporins (introduced in 1960s and 1970s) by the late 1970s. Today, c.50% of S-aureus isolated from US hospitals are resistant to methicillin. The next defence against methicillin-resistant S-aureus (called MRSA) is vancomycin. However, increasing use of vancomycin may lead to the evolution of vancomycin-resistant SA (VRSA).

According to the CDC, c.33% of people carry staph in their nose, usually without any illness and 2% carry MRSA. In the majority of cases, the colonising bacteria do not cause disease. However, damage to the skin or injury may lead to infection. More than 80,000 severe MRSA infections occurred in the US in 2011, with c.11,000 deaths. An estimated 30,800 fewer invasive MRSA infections occurred in the US in 2011 than in 2005 partly because of prevention practices at hospitals and home care. Also, in 2011, fewer infections occurred among patients during hospitalisation than among persons in the community (source: CDC).

Treatment

Draining a skin infection by a healthcare provider may be the only treatment needed for a skin MRSA infection that has not spread. However, severe MRSA infections are harder to treat and a lab test is used to determine the antibiotic to treat the infection. MRSA does not respond to many common drugs like methicillin, amoxicillin, penicillin, oxacillin and cephalorsporins. Hence, doctors may use clindamycin, trimethoprim-sulfamethoxazole, or linezolid. Severe infection can be treated intravenously with Vancomycin.

Containment is key

The best way to prevent the risk of MRSA infection is to maintain good personal hygiene. This includes washing hands often and cleaning the body regularly. Also, cuts, scrapes and wounds should be kept clean and covered until healed. People should avoid sharing personal items, such as towels and razors. It is important to obtain care early if an infection is suspected. Patients with MRSA should be put in a private room whenever possible. All hospital rooms and medical equipment should be cleaned carefully and often. Healthcare providers should wear gloves and a protective gown over their clothing while caring for a patient with MRSA.

Treatments under development

The FDA has approved three new antibiotics for treatment of MRSA in 2014: Dalvance (dalbavancin) and Orbactiv (oritavancin) and Sivextro (tedizolid phosphate).

Middle East respiratory syndrome (MERS)

Middle East respiratory syndrome (MERS) is a viral respiratory infection caused by a newly identified MERS-coronavirus (MERS-CoV) which is derived from bats.

Symptoms

A typical case of MERS consists of fever, cough, and shortness of breath. Pneumonia is a common finding on examination. Gastrointestinal symptoms, including diarrhoea, have also been reported. Severe illness can cause respiratory failure that requires mechanical ventilation and support in an intensive‐care unit. Some patients have had organ failure, especially of the kidneys, or septic shock. Approximately 27% of patients with MERS have died. The virus appears to cause more severe disease in people with weakened immune systems, older people, and those with such chronic diseases as diabetes, cancer, and chronic lung disease.

Infection and transmission

It is not yet understood exactly how people become infected with MERS‐CoV. In some cases, the virus appears to pass from an infected person to another person in close contact. This has been seen among family members, patients, and health‐care workers. Recently, there have been an increased number of reports of health care‐associated infections. In some communities, people have become ill but no potential source of infection has been found. It is possible that these persons were infected by exposure to an animal or perhaps another source or person.

The full picture on the source of MERS is not yet clear. Strains of MERS‐CoV that match human strains have been isolated from camels in Egypt, Qatar, and Saudi Arabia. These and other studies have found MERS‐CoV antibodies in camels across Africa and the Middle East. Human and camel genetic sequence data demonstrate a close link between the virus found in camels and that found in people. It is possible that other reservoirs exist. However, other animals, including goats, cows, sheep, water buffalo, swine, and wild birds, have been tested for antibodies to MERS‐CoV, but so far none have been found in these animals. These studies combined support the premise that camels are a likely source of infection in humans.

Outbreaks

MERS was first reported in 2012 after genome sequencing of a virus isolated from sputum samples from patients who fell ill in a 2012 outbreak of a new flu. By mid-2014, cases have been reported in >20 countries, including: Jordan, Kuwait, Oman, Qatar, Saudi Arabia, the United Arab Emirates, and Yemen (Middle East); France, Germany, Greece, Italy, and the United Kingdom (UK) (Europe); Tunisia and Egypt (Africa); Malaysia and the Philippines (Asia); and the United States of America (Americas).

The virus appears to be circulating widely throughout the Arabian Peninsula. All recent cases that have been reported outside the Middle East first developed infection in the Middle East; then the cases were exported outside the region.

Treatment

No vaccine or specific treatment is currently available. Treatment is supportive and based on the patient's clinical condition.

Although MERS-CoV has been shown to antagonise endogenous IFN production, treatment with exogenous types I and IIIIFN (IFN-α and IFN-λ, respectively) have effectively reduced viral replication in vitro. When rhesus macaques were given interferon-α2b and ribavirin and exposed to MERS, they developed less pneumonia than control animals. Interferon-α2b and ribavirin treatment has been attempted unsuccessfully, albeit late in the onset of the disease. Another proposed therapy is inhibition of viral protease.

Prevention is key

The World Health Organization advises avoiding contact with camels and to eat only fully cooked camel meat, pasteurised camel milk, and to avoid drinking camel urine. The Saudi Ministry of Agriculture has advised people to avoid contact with camels or wear breathing masks when around them.

Plague

Plague is a deadly infectious disease caused by the bacterium Yersinia pestis. Plague is still endemic in some parts of the world.

Pathology: three common types of plague

The symptoms of plague depend on the concentrated areas of infection in each person: bubonic plague in lymph nodes, septicemic plague in blood vessels, pneumonic plague in lungs, and so on. It is treatable if detected early.

- **Bubonic plague** is the most common variety and is primarily an infection of the lymphatic system. It is characterised by swollen and painful lymph nodes or buboes as they have come to be known. Fatality rates are approximately 50% if left untreated.
- **Septicemic plague** is a result of the bacteria directly affecting the bloodstream; it can arise either from direct infection by a carrier flea/rodent or be the result of untreated bubonic as well as pulmonary plague. There is danger of septicemic plague spreading to the lungs resulting in secondary pneumonic plague, which is highly contagious.
- **Pneumonic plague** is the most virulent, the most infectious but also the rarest. As the name suggests, the Yersinia pestis bacteria affects the lungs causing pneumonia. Infection spreads through the inhalation of infected cough droplets emitted by affected individuals or animals. Death can occur within 24 hours of infection.

Symptoms

Bubonic plague is characterised by swollen, painful lymph nodes, usually in the groin, armpit or neck. Fever, chills, headache, and extreme exhaustion are other symptoms. Gangrene, erupting pus-filled glands, and dissolution of the lungs may also occur. A person usually becomes ill with bubonic plague 1-6 days after being infected. If not treated early, the bacteria can spread to other parts of the body and cause septicemic or pneumonic plague. Less common plague syndromes include plague meningitis and plague pharyngitis.

Infection and transmission

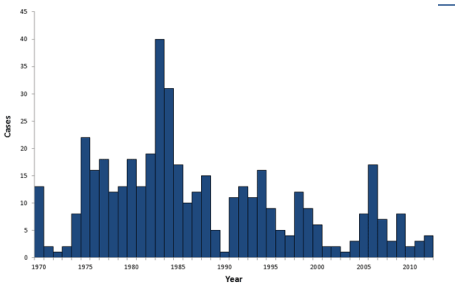
Depending on lung infection, or sanitary conditions, plague can be spread in the air, by direct contact, or by contaminated undercooked food or materials.

Plague is transmitted via droplet contact, direct physical contact, indirect contact, airborne transmission, and faecal-oral transmission. The most common means of transmission from rodents to humans is via the bite of infected rodent fleas. Touching or skinning infected animals without proper precautions may result in contact with contaminated fluid or tissue. In the case of pneumonic plague, the inhalation of droplets from the cough of an infected person or animal is the primary route.

Outbreaks

Human history has witnessed three major plague pandemics. The Justinian Plague in 541 AD killed over 100mn, the Black Death which originated in China in 1334 and spread to Europe where it killed an estimate 60% of the population. The modern plague (1860s) again originated in China and spread to port cities all over the world via steamships causing approximately 10mn deaths.

Exhibit 21: Reported human cases in the U.S. – 1970-2012



Source: CDC

The WHO still receives reports of 1,000-2,000 cases a year and identifies plague as an "emerging disease". In 1994, there was a pneumonic plague epidemic in Surat, India that resulted in 52 deaths and a large internal migration of about 300,000 residents, who fled fearing quarantine.

Table 34: Recent global outbreaks of plague

Aug-2010	Plague in Peru
Aug-2009	Plague in China
Nov-2006	Suspected plague in the Democratic Republic of the Congo
Oct-2006	Plague in the Democratic Republic of the Congo
Jun-2006	Plague in the Democratic Republic of the Congo
Mar-2005	Plague in the Democratic Republic of the Congo - update 4
Jul-2003	Plague in Algeria - Update 2
Jun-2003	Plague in Algeria
Jun-2002	2002 - Plague in Malawi
Feb-2002	2002 - Plague in India
Mar-2001	2001 - Plague in Zambia

Source: Press sources, BofA Merrill Lynch Global Research

Plague in the United States

Since the 1990s most human cases have occurred in Africa. Between 1900 and 2010, 999 human plague cases have occurred in the United States with 80% of them being bubonic. The last urban epidemic occurred in Los Angeles in 1924; since then, reports have been restricted to rural areas. Most human cases have been in the western United States.

Plague as a biological weapon

Plague has a long history as a biological weapon dating back to ancient China, medieval Europe, World War II, and the Cold War between the US and USSR. Aerosolised pneumonic plague remains the most significant threat.

In 1970, the WHO reported that if 50kg of Y. pestis were released as an aerosol over a city of 5 million, pneumonic plague could occur in a 150,000 persons with a mortality rate of over a fifth

Treatment and control

The plague can be easily treated with antibiotics. Early treatment and prophylaxis with streptomycin or gentamicin or the tetracycline/fluoroquinolone classes of antimicrobials is advised. The treatment lasts 10 days, or until two days after the fever subsides. Isolation is essential in the case of pneumonic plague. Fumigation of clothing and other artefacts to kill fleas along with disinfection of sputum and

purulent discharges is also necessary. Although there are no commercially available vaccines against plague, it is possible to vaccinate health workers for short-term protection. Surveillance of the rodent population helps in predicting and controlling outbreaks. Testing blood samples from carnivores who consume rodents is an effective way to sample the underlying rodent population, as testing just a few carnivores is equivalent to testing the hundreds of rodents that are consumed.

Polio

Poliomyelitis (or polio or infantile paralysis) is an acute, viral, infectious disease spread from person to person.

Symptoms

Approximately 90% of polio infections cause no symptoms at all, but affected individuals can exhibit a range of symptoms if the virus enters the blood stream (fever, fatigue, nausea, headache, flu-like symptoms, stiffness in the neck and back, and pain in the limbs). In about 1% of cases, the virus enters the central nervous system, preferentially infecting and destroying motor neurons, leading to muscle weakness and acute flaccid paralysis. Different types of paralysis may occur, depending on the nerves involved. Spinal polio is the most common form, characterised by asymmetric paralysis that most often involves the legs. Bulbar polio leads to weakness of muscles innervated by cranial nerves. Bulbospinal polio is a combination of bulbar and spinal paralysis. One in two hundred infections is followed by paralysis which is irreversible, with 5-10% of people who are paralysed dying when their respiratory muscles are rendered incapable.

Infection and transmission

The mode of transmission is from person to person through the oral or faecal route. In a few cases, it may also be transmitted through contaminated food or water. After entering from either the nose or the mouth, the virus travels to the intestine. After reaching the intestine, it enters the bloodstream where “anti-polio” antibodies are produced. The antibodies in most cases stop the virus from progressing, granting the individual permanent immunity against the disease.

Polio is suspected in cases where individuals experience flaccid paralysis in their limbs, accompanied by muted reflexes for which there is no apparent cause. This should be in conjunction with no apparent sensory or cognitive loss. The virus can be diagnosed based on its recovery from a stool sample. Also, antibodies can be detected in the blood of patients during the early course of infection. The presence of the virus in bodily fluid found in the brain and spine signals detection of paralytic polio.

Outbreaks

Polio was first recognised as a distinct condition in 1840 and was one of the biggest childhood diseases of the 20th century. Since 1988, polio cases have decreased by 99% (from 350,000 cases in 1988 to 406 cases in 2013). In 2014, only Afghanistan, Nigeria and Pakistan have been in the grip of the polio endemic compared with 125 countries in 1988.

Of the three strains of wild poliovirus (type 1, type 2, and type 3), wild poliovirus type 2 was eradicated in 1999 and case numbers of wild poliovirus type 3 are down to the lowest-ever levels with the last case reported in November 2012 from Nigeria.

In May 2014, the WHO declared a public health emergency of international concern, or PHEIC, due to the renewed spread of polio – the outbreaks of the disease in Asia, Africa and the Middle East were considered "extraordinary".

Table 35: Case breakdown by country

Countries	Year-to-date 2014				Year-to-date 2013				Total in 2013	Date of most recent case
	WPV1	WPV3	W1W3	Total	WPV1	WPV3	W1W3	Total		
Pakistan	145			145	28			28	93	30-Aug-14
Afghanistan	8			8	4			4	14	17-Jun-14
Nigeria	6			6	47			47	53	24-Jul-14
Somalia	5			5	169			169	194	11-Aug-14
Equatorial Guinea	5			5				0	0	03-May-14
Iraq	2			2				0	0	07-Apr-14
Cameroon	5			5				0	4	09-Jul-14
Syria	1			1				0	35	21-Jan-14
Ethiopia	1			1	1			1	9	05-Jan-14
Kenya				0	15			15	14	14-Jul-13
Total	**178**	**0**	**0**	**178**	**264**	**0**		**264**	**416**	
Total in endemic countries	**159**	**0**	**0**	**159**	**79**	**0**		**79**	**160**	
Total outbreak	**19**	**0**	**0**	**19**	**185**	**0**	**0**	**185**	**256**	

Source: WHO

Treatment

Polio cannot be cured; the infected person can only be treated for symptoms and the prevention of further complications. The focus of modern treatment has been on providing relief of symptoms, speeding up recovery and preventing complications. Antibiotics are also administered to prevent infections in weakened muscles in conjunction with moderate exercise and a nutritious diet. Treatment entails long-term rehabilitation, which covers occupational therapy, physical therapy, braces, corrective shoes and even orthopaedic surgery in some cases.

Polio eradication plan

A new Polio Eradication and Endgame Strategic Plan 2013-2018 has been developed as the first of its kind to eradicate all types of polio disease simultaneously – both due to wild poliovirus and due to vaccine-derived polioviruses. The plan would require capital of US$5.5bn.

Polio eradication could save US$40-50bn

Economic models have estimated that complete eradication of polio would save the world US$40-50bn over the next 20 years (mostly in low-income countries).

Severe acute respiratory syndrome (SARS)

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a strain of coronavirus, called SARS-coronavirus (SARS-CoV).

Infection and transmission

The SARS genome was identified in April 2003 by the United States' Centers for Disease Control and Prevention (CDC) and a Canadian laboratory. Scientists were able to demonstrate that the SARS coronavirus was the causative agent as macaques infected with the virus developed the same symptoms as human SARS victims. In late May 2003, studies showed that SARS coronavirus could be

isolated from masked palm civets (animals sold as food in the local market in Guangdong, China). The preliminary conclusion was the SARS virus crossed the xenographic barrier from palm civet to humans. In late 2006, scientists established a genetic link between the SARS coronavirus appearing in civets and humans, bearing out claims that the disease had jumped across species.

Coronaviruses are the same family of viruses that causes the common cold. However, SARS is both contagious and sometimes fatal. SARS primarily spreads by close person-to-person contact. The virus that causes SARS is thought to be transmitted most readily by respiratory droplets produced when an infected person coughs or sneezes. The virus can also spread when a person touches a surface or object contaminated with infectious droplets and then touches his or her mouth, nose, or eye(s). SARS virus may also spread more broadly through the air or by other ways that are not known currently.

Symptoms

SARS is diagnosed based on symptoms and whether or not the person has been in close contact with someone who has the virus, as well as via lab tests. The SARS incubation period ranges from 2-10 days. In most cases, SARS begins with a high fever with temperatures of >38°C (>100.4°F). Other symptoms may also include headache, an overall feeling of discomfort and body aches. Some people also have mild respiratory symptoms at the outset. About 10-20% of patients may have diarrhoea. Most patients develop pneumonia. Serious complications such as respiratory failure, heart failure and liver failure are also a risk, most likely for people over 60 years of age.

Outbreaks

SARS was first identified in China in November 2002. Between November 2002 and July 2003, an outbreak of SARS in southern China caused over 8,000 cases and 775 deaths reported in multiple countries with the majority of cases in Hong Kong – with a 9.6% fatality rate according to the WHO. By early 2003, it had spread to three dozen countries in North America, South America, Europe and Asia before it was contained. Since then, there have been four cases of SARS, with three caused by breaches in laboratory biosafety while the fourth incident was due to exposure to animal or environmental sources. According to the WHO, it remains very difficult to predict when or whether SARS will re-emerge in epidemic form.

Table 36: Probable SARS cases*

Number of cases	8,096
Number of deaths	774
Case fatality ratio (%)	9.6
Number of imported cases	142
Number of Health Care Workers affected	1,706

Source: WHO * = From 1 November 2002 to 31 July 2003

Economic impact

With the outbreak of SARS, customers stayed away from stores and restaurants in areas where cases were reported, and travellers cancelled or postponed trips. As a result, industries that offered services, like restaurants, hotels, airlines or cinemas, along with their suppliers were hit particularly hard. Many airlines had to cut their capacity.

The worst economic effects of SARS occurred in Asia as the WHO recommended individuals suspend travel to Hong Kong and Guangdong Province of China, unless absolutely necessary. Hotel occupancy was down to 20% in Singapore and even lower at many Hong Kong hotels. Retail sales also halved in both cities However, every market in the global economy was impacted directly or indirectly by the epidemic.

Treatment and control

There is no cure or protective vaccine for SARS that is safe for use in humans. Healthcare workers treat symptoms in the same way they handle any other unknown form of atypical pneumonia. People with severe cases of SARS and pneumonia may be hospitalised. Generally symptoms are treated to lower fever or ease breathing, using supplemental oxygen and drugs called bronchodilators, which open airways. Antibiotics and antivirals are also used.

Although the causative agent has now been identified, more research is needed as there is no consensus on cure or a protective vaccine for SARS that is safe for use in humans.

Containment is key

Suspected cases of SARS must be isolated, preferably in negative pressure rooms. Complete barrier nursing precautions are taken for any necessary contact with patients. The isolation is 10 days after their symptoms have improved. SARS is most contagious during the second week of illness.

Smallpox

Smallpox is an infectious disease caused by either of two virus variants, Variola major and Variola minor.

Symptoms

Smallpox is localised in small blood vessels of the skin and in the mouth and throat. In the skin it results in a characteristic maculopapular rash and, later, raised fluid-filled blisters. V. major produced a more serious disease and had an overall mortality rate of 30–35%. V. minor caused a milder form of disease (also known as alastrim, cottonpox, milkpox, whitepox, and Cuban itch) which killed about 1% of its victims. Long-term complications of V. major infection included characteristic scars, commonly on the face, which occur in 65–85% of survivors. Blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis were less common complications, seen in about 2–5% of cases.

Infection and transmission

The virus is severely contagious and spreads through person-to-person contact and saliva droplets in an infected person's breath. Its incubation period varies between 7 to 17 days and becomes infectious only after the fever develops. The most infectious period is during the first week of illness. The speed of transmission is slower than measles or chickenpox. It is spread primarily to household members and friends as they are confined to beds till the time they are contagious.

Historic and current outbreaks

Smallpox is believed to have emerged in human populations about 10,000 BC and the earliest known traces were found in the mummified body of Pharaoh Ramses V of Egypt. Smallpox – fatal in c30% of cases - was responsible for an estimated 300–500mn deaths during the 20th century – and the WHO estimated that as recently as 1967, 15mn people contracted the disease and that 2mn died in that year. The last known natural case for smallpox was detected in Somalia in 1977, following that the only known cases were due to a laboratory accident in Birmingham in 1978 killing one person.

"Having considered the development and results of the global program on smallpox eradication initiated by WHO in 1958 and intensified since 1967 … Declares solemnly that the world and its peoples have won freedom from smallpox, which was a most devastating disease sweeping in epidemic form through many countries since earliest time, leaving death, blindness and disfigurement in its wake and which only a decade ago was rampant in Africa, Asia and South America." – WHO Resolution WHA33.3 (1980)

Smallpox as a biological weapon

Smallpox has a long history of potential use as a biological weapon dating back to the French and Indian wars in the U.S., WW2, and the Cold War era USSR. Concerns remain that smallpox and programme scientists could be made available to governments or terrorist groups who might wish to use virus as means of biological warfare. Concern has been expressed that artificial gene synthesis could be used to recreate the virus from existing digital genomes, for use in biological warfare. This has led stakeholders to argue that the remaining virus stocks should be destroyed to eliminate the potential biological threat.

Treatment

After vaccination campaigns throughout the 19th and 20th centuries, the WHO certified the eradication of smallpox in 1979. Smallpox is only one of two infectious diseases to have been eradicated.

No drug is currently approved for the treatment of smallpox. However, antiviral treatments have improved since the last large smallpox epidemics, and studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. The drug must be administered intravenously, however, and may cause serious kidney toxicity.

Tuberculosis

Tuberculosis or TB – historically known as phthisis, phthisis pulmonalis, or consumption – is an infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis.

Symptoms

Symptoms include chronic cough with sputum/blood, chest pains, weakness, weight loss, fever and night sweats. Infection of other organs causes a wide range of symptoms.

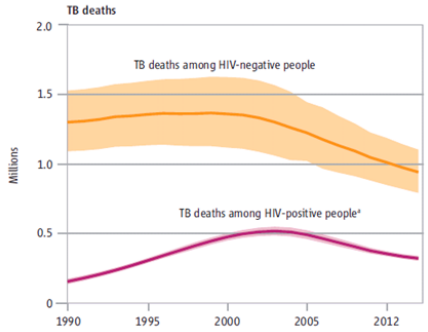
Infection and transmission

Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people with an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. It primarily affects young adults in their most productive years. Most infections do not have symptoms, known as latent tuberculosis. About one in 10 latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those infected.

People with compromised immune systems, such as those with HIV, are particularly at risk. Those co-infected with HIV and TB are 21-34 times more likely to become sick with TB. People with latent TB are just carriers; their bodies are able to fight the bacteria and they do not spread the disease. It is only if and when the latent bacteria become active that it is termed TB disease. Previously contracting the disease, tobacco use, alcohol abuse and diabetes are major risk factors to developing the disease.

The two tests used for diagnosis of the infection are the TB skin test (TST) and TB blood tests. In order to confirm whether the infection has progressed into the disease, sputum sample microscopy or chest x-rays are required. These tests cannot detect latent TB.

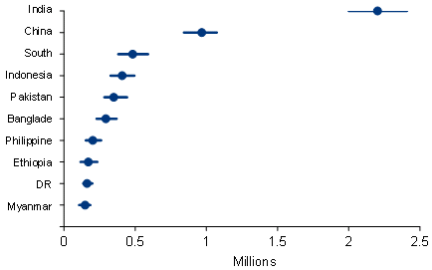
Exhibit 22: Estimated absolute numbers of TB cases and deaths (in millions), 1990–2012



* HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

Source: WHO

Chart 26: Incidence in top 10 countries 2012



Source: WHO

TB is a leading killer of people living with HIV, causing one-fifth of all deaths.

Outbreaks

Tuberculosis has been present in humans since antiquity. One-third of the world's population is thought to have been infected with M. tuberculosis, with new infections occurring in about 1% of the population each year. The absolute number of TB cases has been decreasing since 2006, but TB remains the #2 cause of death worldwide due to a single infectious agent, surpassed only by HIV/AIDS. Annually there are more than 1mn deaths with 8.6mn cases reported in 2012 (source: WHO).

It is estimated that one-third of the world's population has latent TB. The rate of tuberculosis in different areas varies across the globe; about 80% of the population in many Asian and African countries tests positive in tuberculin tests, compared with only 5-10% of the population of the United States. There is a 10% lifetime risk for those who are carriers to develop a full-blown infection. The UN Millennium Development Goal is to reduce deaths by 50% over 1990-2015. The current rate of decline, although quite slow (2% a year), likely puts us on track to achieve the 2015 target.

Treatment

TB is both curable and preventable, although treatment is difficult and requires administration of multiple antibiotics over a long period. A six-month course of four antimicrobial drugs can be used to treat this disease. More than 56mn people worldwide have been treated successfully since 1995. There are 10 drugs currently approved by the US Food and Drug Administration (FDA) for treating TB. Of the approved drugs, the first-line anti-TB agents that form the core of treatment regimens include: isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA). People being treated for TB must complete the regimen with strict adherence to the prescription. Relapses occur if they stop taking the drugs too soon. Again, incorrect usage of the drugs may result in the TB bacteria remaining active and becoming resistant to those drugs. TB that is resistant to drugs is harder and more expensive to treat.

Drug-resistant tuberculosis

Antibiotic resistance is a growing problem in multiple drug-resistant tuberculosis (MDR-TB) infections. Due to the use of standard anti-TB drugs over several decades, there have been documented cases of bacterial strains that are resistant to at least one of the antimicrobial TB drugs. Inappropriate treatment or usage had led to multidrug resistant varieties of TB that do not respond to the two most powerful or "first line" drugs.

Viral hepatitis

Hepatitis is a medical condition defined by the inflammation of the liver and characterised by the presence of inflammatory cells in the tissue of the organ. Viral hepatitis is inflammation of the liver due to a viral infection.

Symptoms

There are several types of hepatitis viruses including types A, B, C, D, E and possibly G. However, types A, B, and C are the most common. Viral hepatitis may be present in acute (short-term) or chronic (long-lasting) forms.

The incubation period for hepatitis virus varies depending on the specific virus. Hepatitis A virus has an incubation period of about 2-6 weeks; Hepatitis B virus from 4-26 weeks, and Hepatitis C virus from about 2-22 weeks. Many patients infected with HAV, HBV and HCV have no/few symptoms of illness.

Symptoms of acute viral hepatitis include fatigue, flu-like symptoms, dark urine, light-coloured stools, fever and jaundice. However, acute viral hepatitis may also occur with minimal symptoms that go unrecognised. Sometimes, acute viral hepatitis causes liver failure (also called fulminant hepatic failure). The symptoms of chronic viral hepatitis are often mild and nonspecific. Hence, these patients can remain undiagnosed for years to decades. Chronic hepatitis can lead to liver cancer and is the most common reason for liver transplantation.

Diagnosis of viral hepatitis is based on symptoms and physical findings as well as blood tests. While acute viral hepatitis can be diagnosed from symptoms, diagnosis of chronic hepatitis can be difficult. There are three types of blood tests for evaluating patients with hepatitis: 1) liver enzymes; 2) antibodies to the hepatitis viruses; and 3) viral proteins or genetic material (viral DNA or RNA).

Transmission and infection

Hepatitis A can be transmitted by eating food or drinking water contaminated with faeces from a person infected with the virus or by anal-oral contact. Hepatitis B can be transmitted by coming into contact with an infected person's blood, semen and other fluids during sex, needles from drug use, etc. Hepatitis C spreads through contact with the blood of an infected person, usually contaminated needles. In countries with poor sanitation, food and water contamination with HAV increases risk. About one-third of all cases of hepatitis comes from an unknown or unidentifiable source, indicating that a person does not have to be in a high-risk group to be infected with a hepatitis virus.

Table 37: Hepatitis viruses

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Transmission	Facial /oral (ingestion of contaminated food and water)	Parental (contaminated food/ body fluids)	Parental	Parental (host must be co-infected with Hepatitis B)	Faecal-oral
Agent	Hepatitis A virus (HAV); Single stranded RNA; no envelope	Hepatitis B virus (HBV); Double stranded RNA; envelope	Hepatitis C virus (HCV); Single stranded RNA; envelope	Hepatitis D virus (HDV); Single stranded RNA; no envelope from HBV	Hepatitis E virus (HEV); Single stranded RNA; no envelope
Incubation Period	2 - 6 weeks	4 - 26 weeks	2 - 22 weeks	Uncertain	2 - 6 weeks
Manifestations or symptoms	Mostly subclinical; severe cases: fever, headache, malaise , jaundice	Frequently subclinical, similar to HAV but fever, headache absent; More likely to progress in severe liver damage	Similar to HBV	Severe lever damage, high mortality rate	Similar to HAV, but pregnant women may have high mortality rate
Chronic liver disease	No	Yes	Yes	Yes	No
Vaccines	2 injections, lifetime protection	3 injections, lifetime protection	None	HBV vaccine is protective as co-infection is required	None

Source: WHO, BofAML Global Research

Outbreaks

In the US, there were an estimated 18,800 new hepatitis B infections and 16,500 new hepatitis C infections in 2011. An estimated 0.8-1.4mn people had chronic hepatitis B and 2.7-3.9mn had chronic hepatitis C in the US at end-2011. Some 5% of adult patients with acute HBV infection and 75-85% of patients with acute HCV infection develop chronic hepatitis (source: CDC). Patients with chronic HBV infection are also at risk of developing cirrhosis, liver failure, and liver cancer. As per the WHO, 130-150mn people worldwide are infected with hepatitis C virus resulting in 350,000 to 500,000 deaths per year.

People most at risk of developing viral hepatitis are workers in the healthcare professions, Asians and Pacific Islanders, sewage and water treatment workers, people with multiple sexual partners, intravenous drug users, HIV patients, and people with haemophilia who receive blood clotting factors.

Treatment

Vaccines are available to prevent hepatitis A and B. Hepatitis A immunity is achieved in 99-100% of persons receiving the two-dose inactivated virus vaccine. The hepatitis A vaccine is not approved for children under one. Vaccines to prevent hepatitis B have been available since 1986 and have been incorporated into most national immunisation programmes for children. Immunity is achieved in greater than 95% of children and young adults receiving the three-dose recombinant virus vaccine. Vaccination within 24 hours of birth can prevent transmission from an infected mother. Adults over 40 have a decreased immune response to the vaccine. The WHO recommends vaccination of all children, particularly of new-borns in countries where hepatitis B is common, to prevent transmission from the mother to child. There is currently no vaccine for hepatitis C or D.

Treatment of acute viral hepatitis involves relieving symptoms of nausea, vomiting, and abdominal pain and maintaining an adequate intake of fluids. Acute HBV is not treated with antiviral drugs. Acute HCV can be treated with drugs used for treating chronic HCV. Treatment of chronic viral hepatitis involves taking medications to prevent further liver damage and eradicating virus.

- **Medications for chronic hepatitis B** infection include injectable alpha, interferons, oral lamivudine (Epivir), oral adefovir (Hepsera), oral entecavir (Baraclude) and oral tenofovir (Viread).
- **Medications for chronic hepatitis C** infection include injectable interferons, oral ribavirin (Rebetol, Copegus). In 2011, FDA also approved oral boceprevir (Victrelis, marketed by Whitehouse Station, N.J.-based Merck) and oral telaprevir (Incivek, marketed by Cambridge, Mass.-based Vertex Pharmaceuticals).

Containment is key

Hepatitis infections can be prevented by avoiding exposure to viruses, using injectable immunoglobulins or by vaccines.

- Avoiding exposure to virus includes taking precautions to prevent exposure to another individual's blood (needles), semen (unprotected sex), and other bodily secretions and waste (stool, vomit).
- Administration of immunoglobulin is called passive protection because antibodies from patients who have had viral hepatitis are given to the patient.

New treatments

- FDA approved Sovaldi (sofosbuvir) tablets in December 2013 for treatment of chronic hepatitis C infection without the need for co-administration of interferon. It was also approved in January 2014 by the European approval authorities. It has been developed by Gilead Sciences.
- FDA approved Olysio (simeprevir) in November 2013 to treat hepatitis C. Olysio is a protease inhibitor that blocks a specific protein needed by the hepatitis C virus to replicate. It is to be used as a component of a combination antiviral treatment regimen. Olysio is marketed by Janssen Pharmaceuticals, based in Raritan, N.J

Appendix – historic list of global epidemics & death counts

Table 38: List of epidemics & death count estimates

Death toll (estimate)	Location	Date	Disease	Comment
ca. 30% of population	Europe, Western Asia, Northern Africa	165-180	unknown, symptoms similar to smallpox	Known as Antonine Plague, due to the name of the Roman emperor in power at the time
ca. 40% of population	Europe	541-542	Bubonic plague	Known as Plague of Justinian, due to the name of the Byzantine emperor in power at the time
30% to 70% of population	Europe	1346-1350	Plague	Known as "Black Plague" or Second Plague Pandemic, first return of the plague to Europe after the Justinian plague of the 6th century
	Mexico	1576	Viral haemorrhagic fever	Cocoliztli
	Seneca nation	1592-1596	Measles	
	Spain	1596-1602	Plague	
	South America	1600-1650	Malaria	
	London, England	1603	Plague	
	Egypt	1609	Plague	
30% to 90% of population	Southern New England, especially the Wampananoag people	1616-1619	Unknown cause. Latest research suggests epidemic(s) of leptospirosis with Wil syndrome. Classic explanations include yellow fever, bubonic plague, influenza, smallpox, chickenpox, typhus and syndemic infection of hepatitis B and hepatitis D	
280,000	Italy	1629-1631	Plague	Italian plague of 1629-1631
	Ontario	1630	Smallpox	Wyandot people
	Thirteen Colonies	1633	Smallpox	Plymouth Colony
	Thirteen Colonies	1634	Smallpox	Connecticut River area
	England	1636	Plague	Newcastle
	China	1641-1644	Plague	Helped end the Ming Dynasty
	Spain	1647-1652	Plague	Great Plague of Seville
	South America	1648	Yellow Fever	
	Italy	1656	Plague	Naples
	Thirteen Colonies	1657	Measles	Boston, Massachusetts
24,148	Netherlands	1663-1664	Plague	Amsterdam
100,000	England	1665-1666	Plague	Great Plague of London
40,000	France	1668	Plague	
	Spain	1676-1685	Plague	
	Austria	1679	Plague	Great Plague of Vienna
	Thirteen Colonies	1687	Measles	Boston, Massachusetts
	Thirteen Colonies	1690	Yellow Fever	New York City
	Canada, New France	1702-1703	Smallpox	
	Sweden	1710-1711	Plague	Stockholm
	Thirteen Colonies	1713	Measles	Boston, Massachusetts
	Thirteen Colonies	1713-1715	Measles	New England and the Great Lakes
	Canada, New France	1714-1715	Measles	
	France	1720-1722	Plague	Great Plague of Marseille
	Thirteen Colonies	1721-1722	Smallpox	Boston, Massachusetts
	Thirteen Colonies	1729	Measles	Boston, Massachusetts
	Spain	1730	Yellow Fever	Cadiz
	Thirteen Colonies	1732-1733	Influenza	
	Canada, New France	1733	Smallpox	
	Balkans	1738	Plague	Great Plague of 1738
	Thirteen Colonies	1738	Smallpox	South Carolina
	Thirteen Colonies	1739-1740	Measles	Boston, Massachusetts
	Italy	1743	Plague	Messina
	Thirteen Colonies	1747	Measles	CT, NY, PA, SC
	North America	1755-1756	Smallpox	
	North America	1759	Measles	
	North America, West Indies	1761	Influenza	
	Pacific Northwest natives	1770s	Smallpox	

Table 38: List of epidemics & death count estimates

Death toll (estimate)	Location	Date	Disease	Comment
	Russia	1770-1772	Plague	Russian plague of 1770-1772
	North America	1772	Measles	
	North America	1775	Unknown cause	Particularly in the Northeast
	England	1775-1776	Influenza	
	Spain	1778	Dengue Fever	Cadiz
	Plains Indiana	1780-1782	Smallpox	North American Smallpox Epidemic
	Pueblo Indians	1788	Smallpox	
	United States	1788	Measles	Philadelphia and New York
	New South Wales, Australia	1789-1790	Smallpox	Amongst the Aborigines
	United States	1793	Influenza and Epidemic Typhus	Vermont
	United States	1793	Influenza	Virginia
	United States	1793-1798	Yellow Fever	Yellow Fever Epidemic of 1793, resurgences
	Spain	1800-1803	Yellow Fever	
	Ottoman Empire, Egypt	1801	Bubonic Plague	
	United States	1803	Yellow Fever	New York
	Egypt	1812	Plague	
	Ottoman Empire	1812	Plague	Istanbul
	Malta	1813	Plague	
	Romania	1813	Plague	Bucharest
	Ireland	1816-1819	Typhus	
>100,000	Asia, Europe	1816-1826	Cholera	First cholera Pandemic
	United States	1820-1823	Fever	Arising near Schuylkill River
	Spain	1821	Yellow Fever	Barcelona
	New South Wales, Australia	1828	Smallpox	Amongst the Aborigines
	Netherlands	1829	Malaria	Groningen Epidemic
	South Australia	1829	Smallpox	
	Iran	1829-1835	Bubonic Plague	
>100.000	Asia, Europe, North America	1829-1851	Cholera	Second Cholera Pandemic
	Egypt	1831	Cholera	
	Plains Indiana	1831-1834	Smallpox	
	England, France	1832	Cholera	London, Paris
	North America	1832	Cholera	Montreal and other cities
	United States	1833	Cholera	Columbus, Ohio
	United States	1834	Cholera	New York City
	Egypt	1834-1836	Bubonic plague	
	United States	1837	Typhus	Philadelphia
	Great Plains	1837-1838	Smallpox	1837-38 Smallpox Epidemic
	Dalmatia	1840	Plague	
	South Africa	1840	Smallpox	Cape Town
	United States	1841	Yellow Fever	Especially severe in the South
	United States	1847	Yellow Fever	New Orleans
20,000+	Canada	1847-1848	Epidemic Typhus	Typhus epidemic of 1847
	Worldwide	1847-1848	Influenza	
	Egypt	1848	Cholera	
	North America	1848-1849	Cholera	
	United States	1850	Yellow Fever	
	North America	1850-1851	Influenza	
	United States	1851	Cholera	Illinois, the Great Plains and Missouri
	United States	1852	Yellow Fever	New Orleans
1,000,000	Russia	1852-1860	Cholera	Third Cholera Pandemic
	Argentina	1852-1871	Yellow Fever	Buenos Aires
	Ottoman Empire	1853	Plague	What is now Yemen
616	England	1854	Cholera	Broad Street Cholera Outbreak
	United States	1855	Yellow Fever	
	Worldwide	1855-1950	Bubonic plague	Third Pandemic
	Portugal	1857	Yellow Fever	Lisbon
	Victoria, Australia	1857	Smallpox	

Table 38: List of epidemics & death count estimates

Death toll (estimate)	Location	Date	Disease	Comment
	Europe, North America, South America	1857-1859	Influenza	
	Middle East	1863-1879	Cholera	Fourth Cholera Pandemic
	Egypt	1865	Cholera	
	Russia, Germany	1866-1867	Cholera	
	Australia	1867	Measles	Sydney
	Iraq	1867	Plague	
	Germany	1870-1871	Smallpox	
40,000	Fiji	1875	Measles	
	Russian Empire	1877	Plague	Baku, now part of Azerbaijan
	Egypt	1881	Cholera	
>9,000	India, Germany	1881-1896	Cholera	Fifth Cholera Pandemic
3,164	Montreal	1885	Smallpox	
1,000,000	Worldwide	1889-1890	Influenza	1889-1890 Flue Pandemic
	Congo Basin	1896-1906	Trypanosomiasis	
>800,000	Europe, Asia, Africa	1899-1923	Cholera	Sixth Cholera Pandemic
	West Africa	1900	Yellow Fever	
113	San Francisco	1900-1904	Bubonic Plague	Third Plague Pandemic
	Uganda	1900-1920	Trypanosomiasis	
	Egypt	1902	Cholera	
	India	1903	Plague	
	China	1910-1912	Bubonic Plague	Manchuria
75,000,000	Worldwide	1918-1920	Influenza	1918 Flu Pandemic
	Russia	1918-1922	Typhus	
	Egypt	1942-1944	Malaria	
	China	1946	Bubonic Plague	Manchuria
	Egypt	1946	Relapsing Fever	
	Egypt	1947	Cholera	
2,000,000	Worldwide	1957-1958	Influenza	Asian Flu
	Worldwide	1961-present	Cholera	Seventh Cholera Pandemic
1,000,000	Worldwide	1968-1969	Influenza	Hong Kong Flu
5	Netherlands	1971	Poliomyelitis	Staphorst, Elspeet and Uddel
	Yugoslavia	1972	Smallpox	1972 outbreak of smallpox in Yugoslavia
	United States	1972-1973	Influenza	London Flu
15,000	India	1974	Smallpox	1974 smallpox epidemic of India
>30,000,000	Worldwide	1981-present	HIV/AIDS	HIV/AIDS pandemic
	South America	1990s	Cholera	
52	India	1994	Plague	1994 Plague Epidemic in Surat
	West Africa	1996	Meningitis	
	Central America	2000	Dengue Fever	
	Nigeria	2001	Cholera	
	South Africa	2001	Cholera	
775	Asia	2002-2003	SARS coronavirus	SARS
	Algeria	2003	Plague	
	Afghanistan	2004	Leishmaniasis	
	Bangladesh	2004	Cholera	
	Indonesia	2004	Dengue Fever	
	Senegal	2004	Cholera	
	Sudan	2004	Ebola	
19	Singapore	2005	Dengue Fever	2005 Dengue outbreak in Singapore
	Mali	2005	Yellow Fever	
50+	India	2006	Dengue Fever	2006 Dengue outbreak in India
50+	Pakistan	2006	Dengue Fever	2006 Dengue outbreak in Pakistan
	Angola	2006	Cholera	Luanda
	Congo	2006	Plague	Ituri Province
	India	2006	Malaria	
	India	2006	Chikungunya virus	Chikungunya outbreaks
	Philippines	2006	Dengue Fever	
49	India	2007	Cholera	
10	Iraq	2007	Cholera	2007 Iraq cholera outbreak

Table 38: List of epidemics & death count estimates

Death toll (estimate)	Location	Date	Disease	Comment
	Congo	2007	Ebola	Mweka
	Ethiopia	2007	Cholera	
	Nigeria	2007	Poliomyelitis	
	Puerto Rico, Dominican Republic, Mexico	2007	Dengue Fever	
	Somalia	2007	Cholera	
	Uganda	2007	Ebola	
	Vietnam	2007	Cholera	
	Brazil	2008	Dengue Fever	
	Cambodia	2008	Dengue Fever	
	Chad	2008	Cholera	
	China	2008	Hand, Foot and Mouth Disease	
	Madagascar	2008	Bubonic Plague	
	Philippines	2008	Dengue Fever	
	Vietnam	2008	Cholera	
4,293	Zimbabwe	2008-2009	Cholera	2008-2009 Zimbabwean cholera outbreak
18	Bolivia	2009	Dengue Fever	2009 Bolivian dengue fever epidemic
	India	2009	Hepatitis B	2009 Gujarat hepatitis outbreak
	Queensland, Australia	2009	Dengue Fever	
	Worldwide	2009	Mumps	Mumps outbreak in the 2000s
931	West Africa	2009-2010	Meningitis	2009-2010 West African meningitis outbreak
14,286	Worldwide	2009-2010	Influenza	2009 flu pandemic
6,500+ (Jan 2012)	Hispaniola	2010-present	Cholera	2010-2011 Haiti cholera outbreak
81	Vietnam	2011-present	Hand, Foot and Mouth Disease	
350+	Pakistan	2011-present	Dengue Fever	2011 dengue fever outbreak in Pakistan
	Congo	2011-present	Measles	
2,296 (Sept 2014)	Guinea, Liberia, Nigeria, Senegal, Sierra Leone	2013-present	Ebola	Ebola virus epidemic in West Africa

Source: Wikipedia !!

Table 39: Companies Mentioned

Companies Mentioned	ML Ticker	Rating	Currency	Price	Footnotes
3M	MMM	B-1-7	USD	144.88	Bbgijopsvw
ABAXIS	ABAX	C-2-7	USD	52.8	Bbp
Abbott Labs	ABT	A-2-7	USD	42.63	Bbijopsvw
AbbVie	ABBV	B-1-7	USD	59.05	BObijopsvw
ACE Limited	ACE	B-1-7	USD	106.59	Bbijopsvw
Actavis	ACT	C-1-9	USD	248	Bbijopsvw
Aegon	AEG	B-1-7	USD	8.47	Bbijopsv
Aflac Inc	AFL	B-1-7	USD	58.62	Bbijopsv
AIA	AAIGF	C-1-8	HKD	41	ijopqv
AIG	AIG	C-1-7	USD	54.99	BObijopsv
Airgas, Inc.	ARG	B-3-7	USD	113.19	Bbgijopsv
AJ Gallagher	AJG	B-1-7	USD	45.46	Bbgijopsvw
Allstate Corp.	ALL	B-1-7	USD	61.68	Bbgijopsv
Amer Fincl Grp	AFG	B-1-7	USD	58.87	Bbgijopsv
Ansell	ANSLF	B-2-7	AUD	19.48	ijopqsv
Aon Corporation	AON	B-2-7	USD	87.29	BObgijopsv
Arch Capital	ACGL	B-2-9	USD	54.53	Bbijopsv
Ashford Hospitality	AHP	C-1-7	USD	15.06	Bbgijps
Aspen	APNHF	B-2-7	ZAR	332.78	ijopqsvw
Assurant Inc.	AIZ	B-3-7	USD	65.47	Bbijopv
Astellas Pharma	ALPMF	B-1-7	JPY	1615	ijopqv
AstraZeneca	AZN	B-2-7	USD	71.66	Bbijopsv
Aurobindo Pharma	XLZFF	C-1-7	INR	799.15	qz
Aviva plc	AIVAF	B-1-8	GBP	522.5	ijopv
Axis Capital	AXS	B-1-7	USD	48.26	Bbijopsvw
Baxter	BAX	B-1-7	USD	72.16	Bbijopsvw
Bayer	BAYRY	B-1-7	USD	143.96	Bbgijopqsv
Becton Dickinson	BDX	A-2-7	USD	113.72	Bbjop
Boyd Gaming Corp	BYD	C-3-9	USD	10.51	BObgijpsv
Bristol-Myers Squibb	BMY	A-2-7	USD	51.96	Bbgijopsvw
BTSGIF	XYIYF	B-1-8	THB	9.85	q
Cadila Health	CDLHF	C-1-7	INR	1276.75	ijopqsvz
Caesars	CZR	C-3-9	USD	13.62	BObijopsv
Cardinal Health	CAH	B-1-7	USD	77.66	Bbijopsvw
CareFusion	CFN	C-1-9	USD	46.46	Bbgijopsv
Carnival	CCL	B-1-7	USD	41.12	Bbgijoprsvw
Carnival	CUKPF	B-1-7	GBP	2451	Ngijoprsv
Catalent, Inc.	CTLT	C-1-9	USD	24.84	Bbgjp
Cathay FHC	CHYYF	B-2-7	TWD	50	ijopqvz
Cepheid Inc	CPHD	C-2-9	USD	44.79	Bbw
China Life	CHLJF	C-1-7	TWD	25.95	ijoqvz
Choice Hotels	CHH	C-3-8	USD	52.63	Bbijops
Chubb Corp	CB	A-2-7	USD	91.62	Bbijopsvw
Cipla	XCLAF	C-1-7	INR	600	iqvz
CNA Financial	CNA	C-1-7	USD	38.32	Bbijops
Cremer	COQEF	C-1-9	BRL	17.09	ijoqvz
CSL Ltd	CMXHF	B-1-7	AUD	74.6	ijopqsv
CSPC Pharma	CHJTF	B-2-8	HKD	6.8	iqsv
Cubist	CBST	C-1-9	USD	68.02	Bbjop
CVC	XTFVF	C-1-7	BRL	15.9	giqsz
Daiichi Sankyo	DSKYF	B-3-7	JPY	1835	ijopqsv
Daqin Railway	DAQIF	B-1-7	CNY	7.84	q
DiamondRock	DRH	C-3-7	USD	12.9	Bbjp
DuPont	DD	B-1-7	USD	72.83	Bbijopsvw
Durata	DRTX	C-1-9	USD	13.95	Bbijops
Ecolab Inc	ECL	A-1-7	USD	117.63	Bbijopsvw
Endurance	ENH	C-2-7	USD	55.99	Bbjopw
FelCor	FCH	C-3-7	USD	9.43	Bbijpv
FirstGroup Plc	FGROF	C-1-9	GBP	118	ijopqsv
Flight Centre	FGETF	C-1-7	AUD	43.67	ijpqsv
FUJIFILM	FUJIF	B-1-7	JPY	3424.5	ijopqsv
GlaxoSmithKline	GLAXF	A-2-7	GBP	1428.5	ijpv

Table 39: Companies Mentioned

Companies Mentioned	ML Ticker	Rating	Currency	Price	Footnotes
Go-Ahead Group	GHGUF	B-1-7	GBP	2488	Bbq
Grifols - A	GIFLF	B-1-7	EUR	32.315	ijpqsv
Guangshen Railway	GNGYF	C-1-8	HKD	3.1	
Hannover Re	HVRRF	B-3-7	EUR	63.97	Bbijopqv
Hersha Hospitality	HT	C-2-7	USD	6.43	Bbijopv
Hikma	HKMPF	B-2-7	GBP	1660	BNbijopqv
Honeywell	HON	B-1-7	USD	93.83	Bbgijopsvw
HongkongandShanghai	HKSHF	B-3-8	HKD	11.76	q
Hospira Inc.	HSP	C-2-9	USD	53.04	Bbijpv
Host Hotels	HST	C-1-7	USD	21.4	Bbijops
Hoteles City	HCITY	RSTR**	MXN	25.68	iqsvw
Illumina	ILMN	C-1-9	USD	168.64	Bbgijopsvw
Impax Labs	IPXL	C-3-9	USD	24.64	Bbjo
Infinity Ppty	IPCC	C-3-7	USD	65.07	Bbijpsv
Johnson & Johnson	JNJ	A-2-7	USD	108.64	Bbgijopsvw
JR Central	CJPRF	B-1-7	JPY	14880	iqv
JR East	EJPRF	A-1-7	JPY	8269	giqs
JR West	WJRYF	B-3-7	JPY	4982.5	iqv
Keio	KTERF	A-3-7	JPY	836	q
Keisei Railway	KELRF	A-3-7	JPY	1086	q
Kimberly-Clark	KMB	A-2-7	USD	108.86	Bbijopvw
La Quinta Holdings	LQ	C-2-9	USD	19.64	Bbgijopsv
Laboratory Corp	LH	B-1-9	USD	103.88	Bbgijopsvw
LaSalle	LHO	C-1-7	USD	34.72	Bbijpv
Legal & General	LGGNF	B-1-7	GBP	234.7	Nijopqv
Lincoln National	LNC	C-1-7	USD	55.05	Bbijopsvw
Lupin Limited	LPMCF	C-1-7	INR	1367.25	qz
Markel Corp.	MKL	B-3-9	USD	633.51	Bbijopv
Marriott Intl.	MAR	C-1-7	USD	71.39	Bbijopsv
Marsh & McLennan	MMC	C-2-7	USD	52.93	Bbgijoprsv
McKesson Corp.	MCK	B-1-7	USD	197.29	Bbgijopsvw
Merck & Co.	MRK	A-1-7	USD	60.36	Bbijopsvw
Merck KGaA	MKGAF	B-3-7	EUR	74	Bbijopqsv
Mercury General	MCY	B-3-7	USD	48.96	Bbjop
MetLife Inc.	MET	B-1-7	USD	55.45	BObgijopsvw
MGM Resorts	MGM	C-1-9	USD	22.81	BObgijopsvw
MTRC	MTRJF	A-2-7	HKD	31.4	ijopqv
Munich Re	MURGF	B-1-7	EUR	155.57	ijopqsv
Mylan Inc.	MYL	C-1-9	USD	46.44	BObgijopsvw
National Express	NXPGF	B-1-7	GBP	244.2	BNbijopqsv
Natl Interstate	NATL	-6-	USD	27.96	Bbijopsv
Novartis	NVSEF	A-2-7	CHF	87.9	ijopsv
Odakyu	ODERF	A-3-7	JPY	1036	q
OneBeacon Insur	OB	C-3-7	USD	15.71	Bbijopv
PartnerRe	PRE	C-1-7	USD	111.31	Bbgijopsv
Pebblebrook	PEB	C-1-7	USD	37.67	Bbgijopsv
Penn Natl Gaming	PENN	C-3-9	USD	11.81	Bbgijopsv
Pfizer Inc.	PFE	A-1-7	USD	30.31	BObgijopsvw
PICC GROUP	XFASF	C-2-7	HKD	3.3	ijoqsv
PICC P&C	PPCCF	C-3-7	HKD	13.96	ijoqsv
Ping An Insura-H	PIAIF	B-1-7	HKD	60.35	q
Pinnacle Ent.	PNK	C-1-9	USD	26.15	BObijopsv
Platinum	PTP	C-3-7	USD	61.47	Bbw
Principal Fincl	PFG	B-1-7	USD	54.29	BObijopsv
Progressive Corp	PGR	B-2-7	USD	25.39	Bbjop
Protective Life	PL	-6-	USD	69.44	Bbijopv
Prudential	PUK	B-1-7	USD	46.41	Bbgijopsv
Prudential Fincl	PRU	B-1-7	USD	91.48	BObgijopsv
Prudential PLC	PUKPF	B-1-7	GBP	1418.5	gijopsv
Qiagen	QGEN	C-2-9	USD	23.74	Bbijopsvw
RenaissanceRe	RNR	C-3-7	USD	100.2	Bbjopw
RLJ Lodging Trust	RLJ	C-2-7	USD	28.63	Bbgijopsvw

Table 39: Companies Mentioned

Companies Mentioned	ML Ticker	Rating	Currency	Price	Footnotes
Roche Holdings	RHHBF	B-1-7	CHF	283.8	ijopqv
Ryman	RHP	C-2-7	USD	48.01	Bbgijopsvw
Sanofi	SNYNF	A-1-7	EUR	88.92	ijopsv
Sawai Pharma	SWPIF	B-2-7	JPY	6290	q
SCOR	SZCRF	B-1-7	EUR	24.69	ijopqv
Selective Ins	SIGI	B-1-7	USD	22.74	Bbijopv
Shangri-la Asia	SHALF	B-2-8	HKD	11.82	iqv
Shin Kong FHC	SKFHF	C-3-9	TWD	9.2	ijopqvz
Siemens	SMAWF	A-1-7	EUR	94.72	ijopqsvw
Sino Biopharma	SBMFF	C-3-7	HKD	8.05	q
Stancorp Fincl	SFG	B-2-7	USD	63.61	Bbjop
Starwood Hotels	HOT	C-1-7	USD	83.63	Bbgijopsvw
Sunstone Hotel Inv	SHO	C-2-7	USD	13.8	Bbgijpsv
Swiss Re	XERSF	B-3-7	CHF	76.3	ijopqsv
Symetra	SYA	C-3-7	USD	23.56	Bbijopv
Teva	TEVA	C-1-7	USD	53.74	Bbijpvw
The Hartford	HIG	C-1-7	USD	37.56	Bbijopvw
The Medicines Co.	MDCO	C-1-9	USD	23.69	Bbis
Theravance Biopharma	TBPH	C-1-9	USD	25.29	Bb
Thermo Fisher	TMO	A-1-7	USD	123.51	Bbgijopsvw
Third Point Re	TPRE	C-1-9	USD	15.05	Bbop
Thomas Cook	TCKGF	C-2-9	GBP	117.1	ijopqv
Tobu Railway	TBURF	A-3-7	JPY	573	q
Tokyu Corp.	TOKUF	B-1-7	JPY	740	iqv
Torchmark	TMK	B-2-7	USD	53.26	Bbijopsv
Travelers Cos	TRV	B-1-7	USD	94.79	#Bbijopsvw
Unum Group	UNM	B-1-7	USD	35.18	Bbgijopsv
Vail Resorts	MTN	C-1-7	USD	86.04	Bbijps
Validus Holding	VR	C-1-7	USD	38.89	Bbijosvw
Voya Financial	VOYA	C-2-7	USD	39.16	Bbgijopsv
W.R. Berkley	WRB	B-1-7	USD	48.16	Bbijopv
West Pharma	WST	A-1-7	USD	44.39	Bbijopv
Willis Group	WSH	C-2-7	USD	41.89	Bb
XL Group	XL	C-1-7	USD	33.78	Bbijoprsv
Zoetis	ZTS	C-1-7	USD	36.58	Bbijopsvw

Source: BofA Merrill Lynch Global Research

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