Influenza:
Master of Changes

Salim Parker

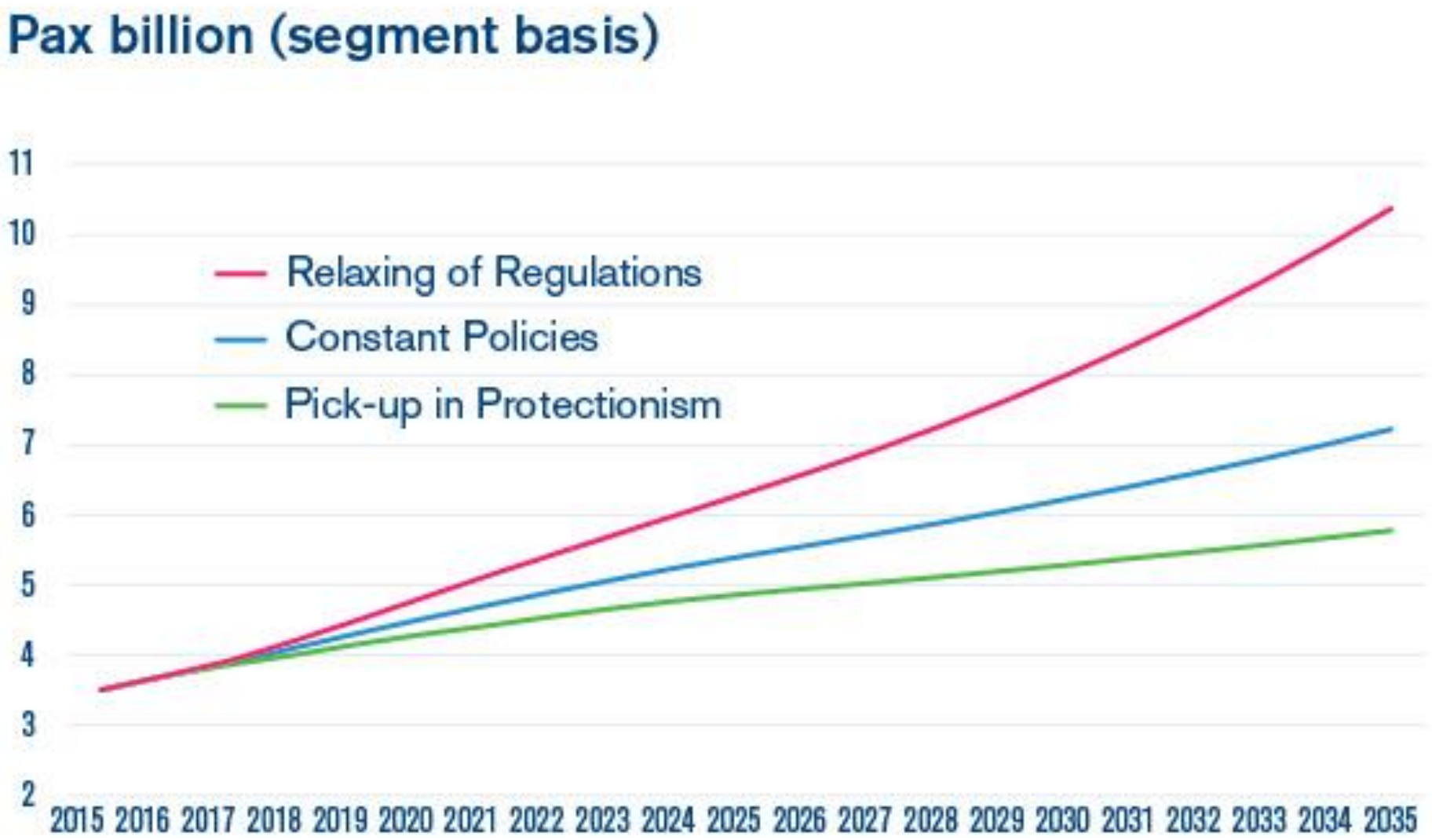
SOUTH AFRICAN SOCIETY OF TRAVEL MEDICINE
SASTM
Guiding the Profession
Protecting the Public

Joshua Lederberg

"The microbe that felled one child in a distant continent yesterday can reach yours today, and seed a global pandemic tomorrow."

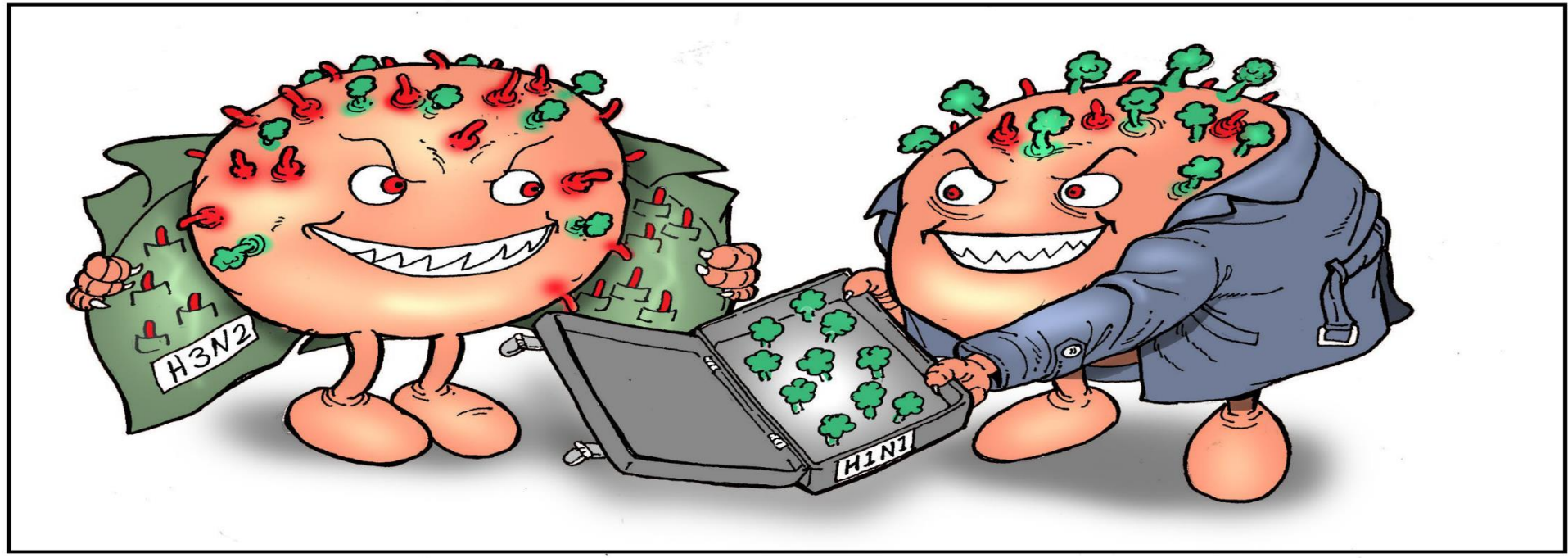

zh
aw
TECINORAMA

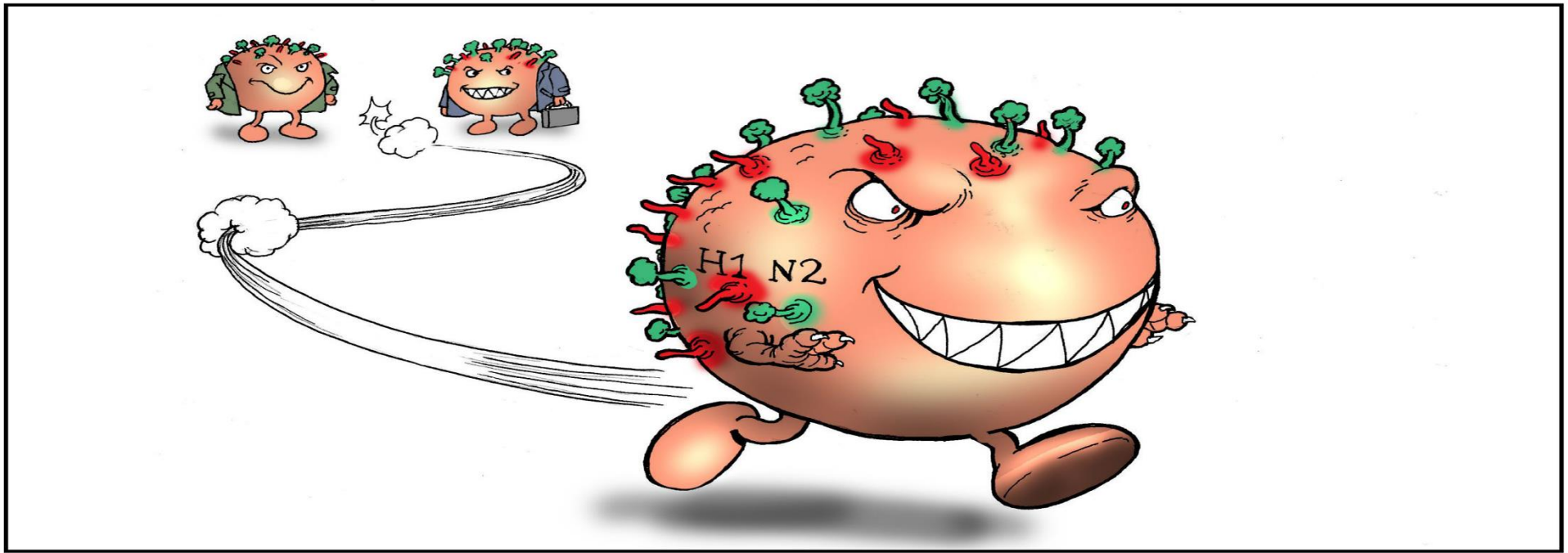
Global Air Passenger Forecast



http://www.iata.org/pressroom/pr/Pages/2016-10-18-02.aspx


N1
N2
N3
N4
NEUROMINIDASE
H1
H2
H3
H4
H5
HAEMAGGLUTIN
H1N2
H5N1
H1N1
H7N9


H3N2
H1N1


H1
N2

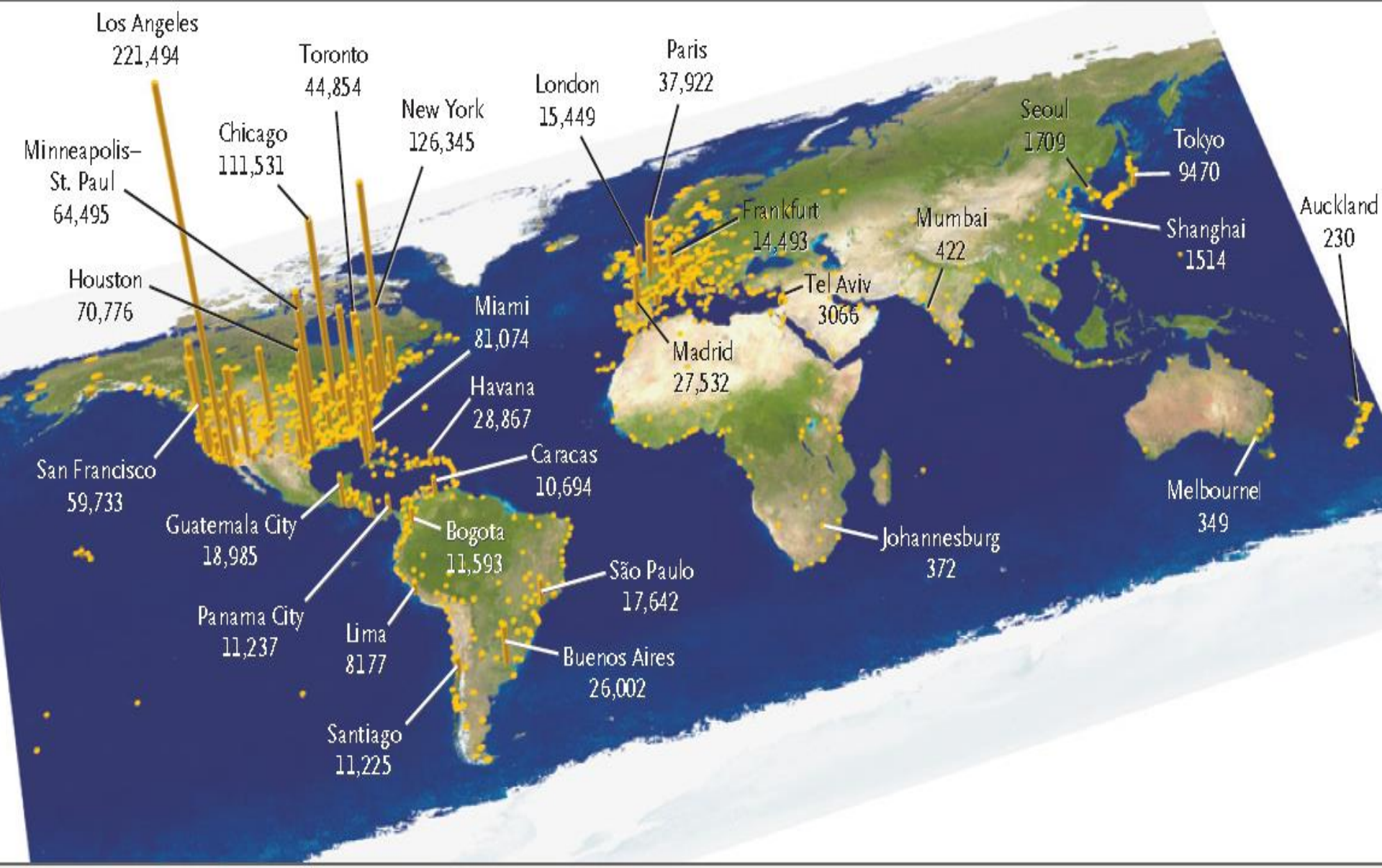
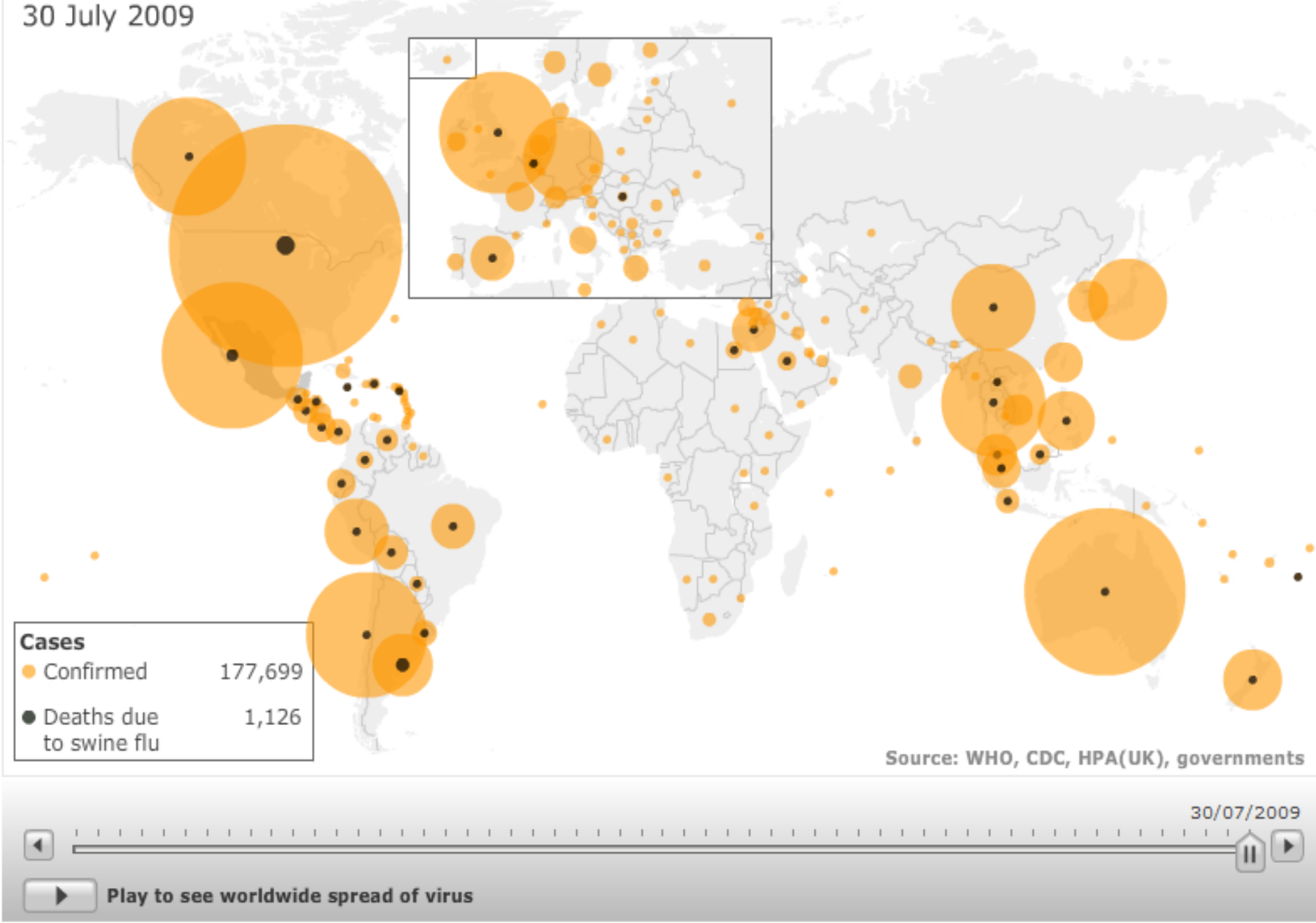


Figure 1. Destination Cities and Corresponding Volumes of International Passengers Arriving from Mexico between March 1 and April 30, 2008.



Source: WHO, ECDC, CPC, HPA (UK), governments

http://news.bbc.co.uk/2/hi/americas/8021547.stm

Ten leading causes of death in South Africa

(www.statssa.gov.za)

Causes of death (based on ICD-10)	2011			2012			2013		
	Rank	Number	%	Rank	Number	%	Rank	Number	%
Tuberculosis (A15-A19)**	1	55 102	10,7	1	48 409	9,9	1	40 542	8,8
Influenza and pneumonia (J09-J18)	2	33 847	6,6	2	26 887	5,5	2	23 727	5,2
Human immunodeficiency virus [HIV] disease (B20-B24)	7	17 338	3,4	6	19 146	3,9	3	23 203	5,1
Cerebrovascular diseases (I60-I69)	3	26 104	5,1	3	24 454	5,0	4	22 463	4,9
Diabetes mellitus (E10-E14)	5	21 147	4,1	5	21 820	4,4	5	22 196	4,8
Other forms of heart disease (I30-I52)	4	23 916	4,6	4	22 352	4,6	6	21 104	4,6
Hypertensive diseases (I10-I15)	8	15 784	3,1	7	16 491	3,4	7	16 754	3,7
Intestinal infectious diseases (A00-A09)	6	19 647	3,8	9	15 225	3,1	8	15 782	3,4
Other viral diseases (B25-B34)	9	14 805	2,9	8	15 301	3,1	9	13 614	3,0
Chronic lower respiratory diseases (J40-J47)	10	13 277	2,6	10	12 464	2,5	10	12 035	2,6
Other natural causes		226 564	44,0		220 021	44,8		200 294	43,6
Non-natural causes		46 955	9,1		48 530	9,9		47 219	10,3

Table 4.5: The ten leading underlying natural causes of death, 2013–2015*

Causes of death (based on ICD-10)	2013			2014			2015		
	Rank	Number	%	Rank	Number	%	Rank	Number	%
Tuberculosis (A15-A19)**	1	41 904	8,8	1	39 495	8,3	1	33 063	7,2
Diabetes mellitus (E10-E14)	5	23 133	4,9	3	23 966	5,0	2	25 070	5,4
Cerebrovascular diseases (I60-I69)	4	23 158	4,9	2	24 131	5,1	3	22 879	5,0
Other forms of heart disease (I30-I52)	6	22 189	4,7	4	22 928	4,8	4	22 215	4,8
Human immunodeficiency virus [HIV] disease (B20-B24)	3	23 825	5,0	6	22 729	4,8	5	21 926	4,8
Influenza and pneumonia (J09-J18)	2	24 345	5,1	5	22 813	4,8	6	20 570	4,5
Hypertensive diseases (I10-I15)	7	17 104	3,6	7	18 319	3,9	7	19 443	4,2
Other viral diseases (B25-B34)	9	14 101	3,0	9	14 508	3,1	8	16 097	3,5
Chronic lower respiratory diseases (J40-J47)	10	12 384	2,6	10	12 690	2,7	9	12 667	2,8
Ischaemic heart diseases (I20-I25)	…	…	…		…	…	10	12 239	2,7
Intestinal infectious diseases (A00-A09)	8	16 163	3,4	8	14 795	3,1	…	…	….
Other natural causes		207 523	43,6		207 593	43,7		202 840	44,1
Non-natural causes		49 681	10,4		50 692	10,7		51 227	11,1
All causes		**475 510**	**100,0**		**474 659**	**100,0**		**460 236**	**100,0**

*Data from 2013–2014 have been updated with late registrations/delayed death notification forms processed in 2015/2016.

** Including deaths due to *MDR-TB* and *XDR-TB*.

… Category not in top ten.

2013 Returning Pilgrims Surveillance

Microbiology Results

171 participants had specimens collection

- 0 NP swabs taken
- 105 OP swabs
- 66 OP swabs & sputum collected
- 23/66 sputum had Bartlett score >1

0 *Bordetella* spp

6 *Neisseria meningitidis* on (sodC) PCR

- 1 on (ctrA) PCR (serogroup B)
- 5 non -groupable

Figure 2: Bacteriological Results

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

2013 Returning Pilgrims Surveillance

Influenza	OP Swabs	Sputum	Both	Total
InfA H3N2	4	2	1	7
InfA H1N1 (pdm09)	1	1	0	2
InfB (Yamagata)	4	1	1	6
InfA H3N3; H1N1 (pdm09)	1	0	0	1
Total	10	4	2	

No MERS-CoV

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Acquisition of pneumococci during Hajj

- **Benkouiten *et al:* 7.3% pre hajj carriage vs 19.5% post hajj 2012**
- **2012: 19% nasal acquisition**
- **2013: 36% pharyngeal acquisition**
- **40%-60% of serotypes covered by PCV13 depending on study**

Clin Microbiol Infect 2015; 395 21(1):77-8.

- **South African pharyngeal study 2015: 10% pre and 25% post hajj carriage (18% post Hajj influenza virus carriage).** **No MERS-CoV**

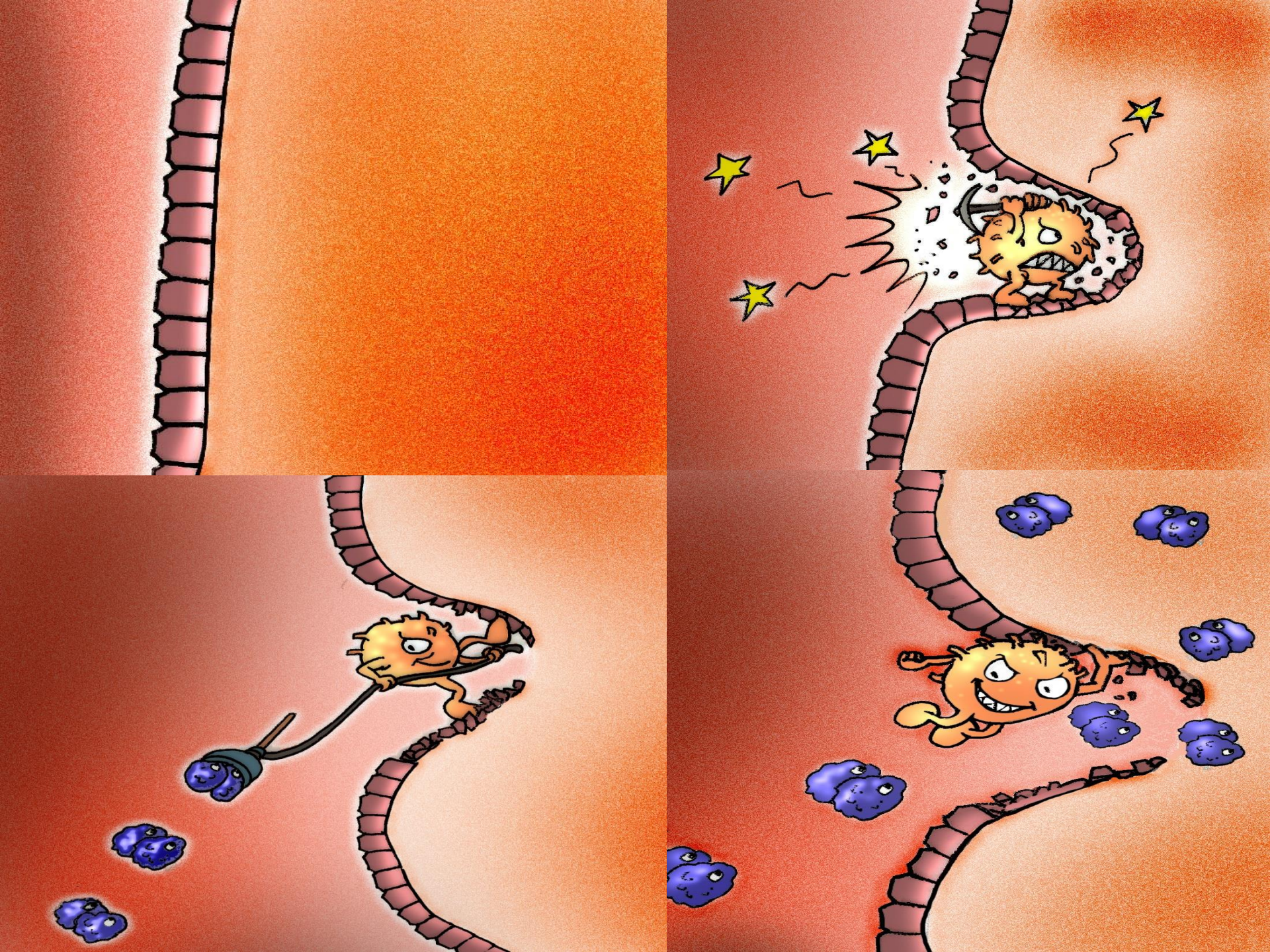
http://myistm.istm.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=de963fa8-fdd9-6461-13c4-2c6c51354710&forceDialog=0 Page 3.

Captain of the Men of Death

Sir William Osler: 100 hundred years ago

- **Pneumococcus killed adolescents and young adults**
- **Caused more deaths than TB at that time**
- **'Friend of the aged': "it kills them gently without severe symptoms"**
- *'To die of pneumonia is almost the natural end of old people..'*

South Afr J Epidemiol Infect 2009;24(4):7-19



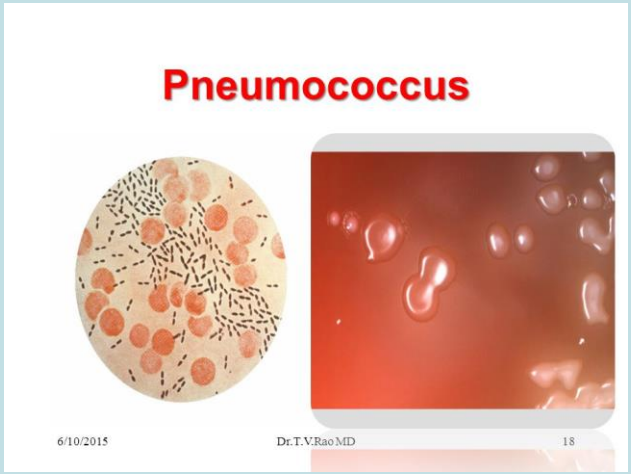
Effects of pneumococcal vaccination

- South African data
- Pre-vaccination
  - 107,600 severe cases annually
  - 5000 deaths annually
- Post-vaccination period (2012-2013)
  - 41 800 severe cases annually
  - 1 900 deaths annually
- Other factors: increased HIV management

PLoS ONE 12(7): e0179905. https://doi.org/10.1371/journal.pone.0179905

The Endless Cycle

LIFE STYLE DISEASES



DVT in Perspective

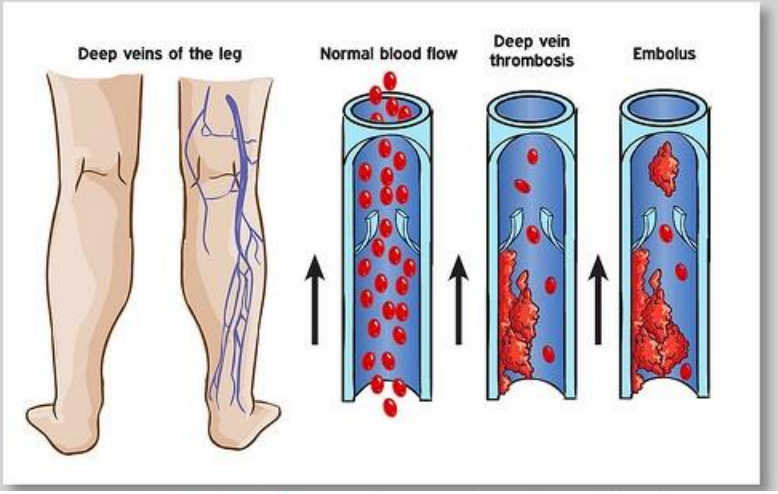
- **In the UK, if**

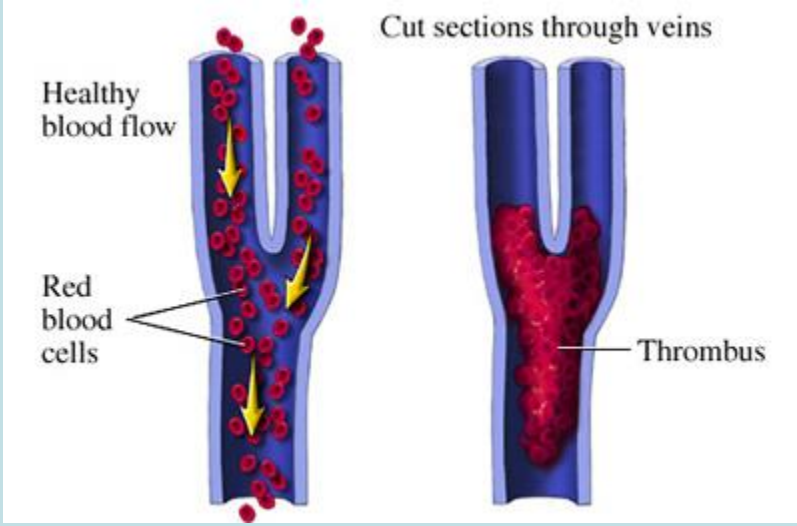
1. **Take all breast cancer deaths.....**
2. **Add all prostate Ca deaths.....**
3. **Add MVA fatalities.....**
4. **Add HIV deaths.....**
5. **Double the total.....**

PE deaths in general population exceeds this number

Pneumonia and DVT

- **Recent pneumonia (one year) 5x higher risk for DVT than controls**
- **Recent pneumonia (months) increases DVT risk during long haul flights**
- **Long haul flight increase risk 2-4 x**
- **Elderly travelers at higher risk for developing DVT**
- **Influenza increases the risk of DVT and PE**





J Thromb Haemost 2012; 10: 1179–82.

M. Goeijenbier et al. / Vaccine 35 (2017) 5095–5101

Table 2: Prevalence of ILI in vaccinated and unvaccinated pilgrims during the 2010 Hajj.

VACCINATION EFFECT ON ILI 2010		
	NUMBER	INFLUENZA LIKE ILLNESS
Vaccinated	318 43.3%	25 7.9% of vaccinated group
Unvaccinated	417 56.7%	54 12.9% of unvaccinated group
TOTAL	**735**	**79** **10.7% of total**

Influenza Vaccine in Pregnancy

- **2116 ladies in South African study**
- **Vaccine 50% efficacy**
- **Influenza vaccine seems to be protective against pertussis**
- **Post study analysis and not part of initial study**
- **Needs further investigations**
- **Influenza increases susceptibility to streptococcus, *Haemophilus influenzae*, and *Staphylococcus aureus infection***

http://www.nejm.org/doi/full/10.1056/NEJMc1705208?query=TOC

25% influenza vaccine uptake in Cape Town HCW

Table 1 Demographics of paediatric healthcare providers (*n*=201)

Variable	Frequency	%
Age, yrs, median, IQR	34	IQR 27–43
Gender (female)	169	84.1
Job category		
Medical doctor	90	44.8
Nurse	95	47.2
Allied health professional*	16	8
Healthcare experience, yrs		
0 (healthcare student)	43	21.4
≤5	18	9
5–10	51	25
≥10	89	44.6

IQR, interquartile range; * allied health professional: dietician, occupational therapist, physiotherapist

- Only 25% of paediatric staff reported receiving annual influenza vaccine
- Younger staff were more likely to be vaccinated
- Medical staff were 19 times more likely to work while ill (presenteeism)

Sliide from **Angela Dramowski**

Original Research Paper

Healthcare-associated infections in children: knowledge, attitudes and practice of paediatric healthcare providers at Tygerberg Hospital, Cape Town

Once upon a Time

IN FACT….

Exactly 100 years ago……

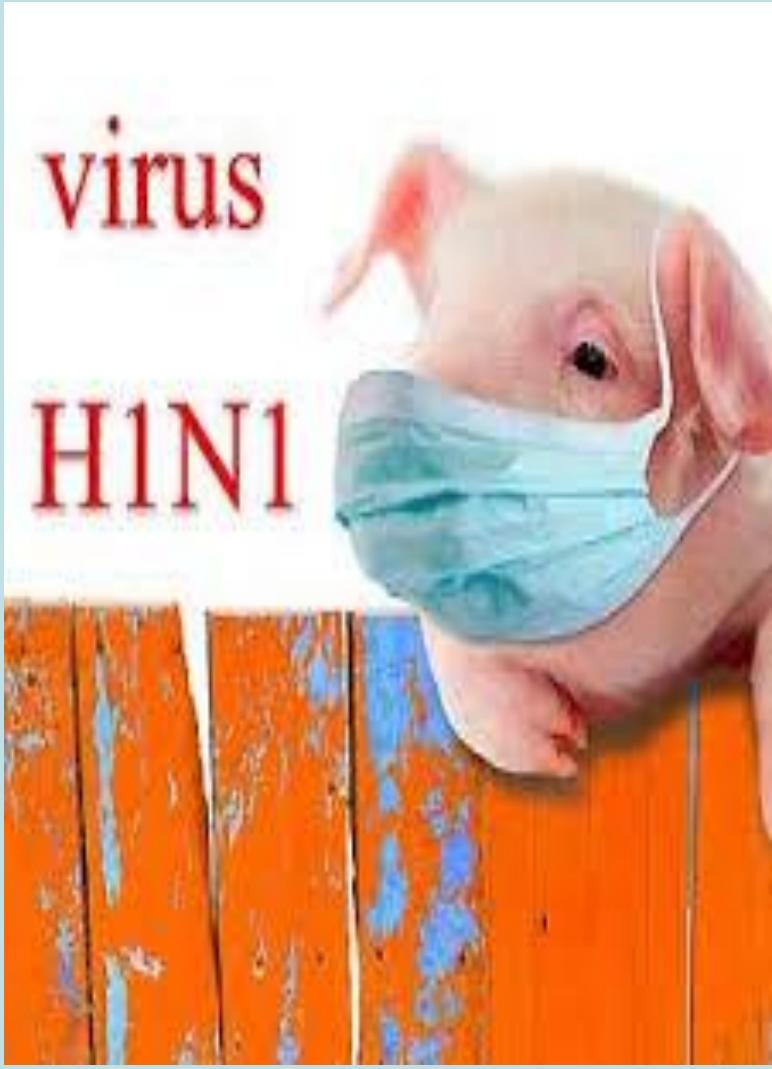
Spanish Flu 1918

- Arrived in South Africa Sept 1918
- Killed mostly the younger generation 18-40 years old
- Up to 500 000 died; 900 000 orphans
- 5th most severely affected country on earth
- Two waves, from Cape Town and Durban
- Spread by well developed transport system

Sunday Times 4 Feb 2018 Pg 14

H1N1 Reverse Zoonosis: Human-Swine

- Humans transmit far more influenza viruses to swine than swine transmit to humans
- Human-to-swine transmission is key to the evolution of influenza diversity in swine
- In effect, humans sow the seeds of future pandemics by infecting pigs
- A balanced view of the bidirectional nature of the human–animal interface is needed



- **Trends in Microbiology:** Volume 23, Issue 3, March 2015, Pages
- http://www.sciencedirect.com/science/article/pii/S0966842X14002467

Influenza Vaccine and Heart Failure

- **Vaccine reduced risk of dying:**
  - **By 50% during influenza season**
  - **By 20% during non-influenza season**
- **22% decreased risk of being hospitalised**
- **Observational studies of 78 000 patients**

https://www.medicalbrief.co.za/archives/flu-injection-lowers-mortality-risk-people-heart-failure/

Influenza and cardiac surgery

- Surgical patients can be asymptomatic
- Acute respiratory distress syndrome (ARDS) following cardiac surgery
  - 5.6% if surgery out of influenza season
  - 9.0% if surgery was during influenza season
  - Mechanical ventilation longer in influenza season
- Influenza season is independent risk factor for developing ARDS during cardiac surgery

February 22, 2018
N Engl J Med 2018; 378:772-773
DOI: 10.1056/NEJMc1712727

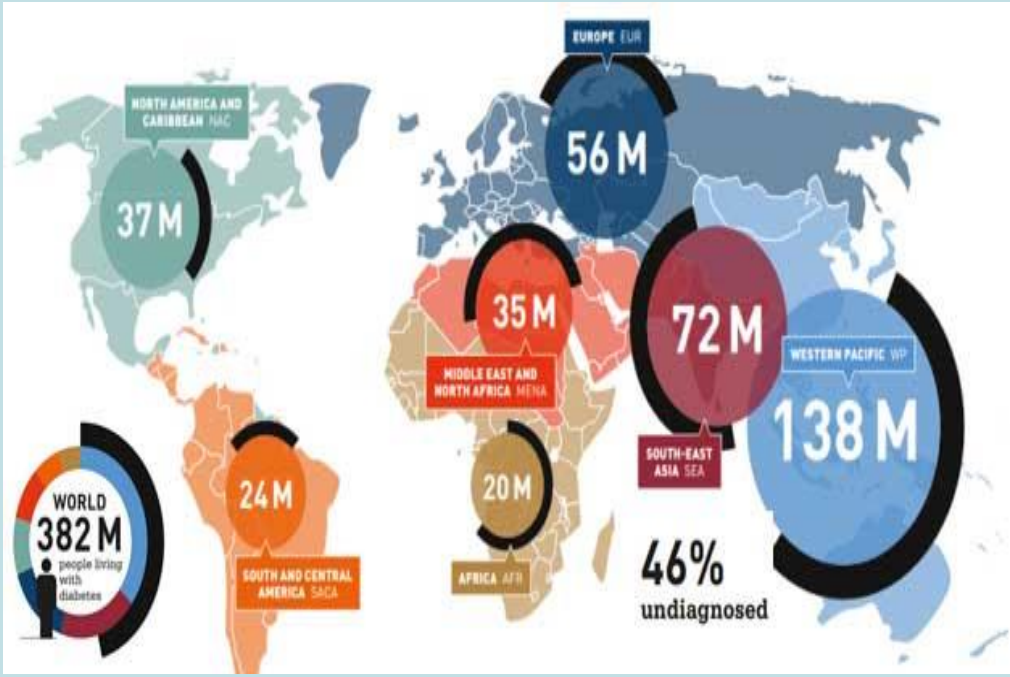
Pneumonia and cardiac disease

- ***Pneumococcal vaccines: the results from a large hospital-based case control study suggest that pneumococcal vaccination was associated with a 50% lower risk of myocardial infarction 2 years after vaccination.***

- *Lamontagne F, Garant MP, Carvalho JC, Lanthier L, Smieja M, Pilon D. Pneumococcal vaccination and risk of myocardial infarction. CMAJ. 2008; 179(8): 7737.*

Diabetes Tsunami hits South Africa

- 3.5 million, about 6% of SA population suffer from diabetes
- Prevalence of diabetes 3.9-8.8% in SA
- Many more undiagnosed
- Estimated that another 5 million have pre-diabetes
- 29% of elderly 'coloureds' in Cape Town have diabetes (genetic?)



SA Fam Pract 2006:48(10)

Slide: Courtesy ShubnumHaniff-Ismail

Source : IDF

Diabetic Epidemic

- **366 million people with diabetes today**
- **552 million in 2030 (3 new diagnoses every 10 seconds)**
- **1 person dies every 7 seconds from diabetes (4.6mil/year)**
- **183 million people are unaware that they have diabetes**
- **At least 78% of people in Africa are undiagnosed and do not know they are living with diabetes.**
- **80% of people with diabetes live in low and middle income countries.**

Slide courtesy
Sr Haniff-Ismail

Influenza and Diabetes

- **Diabetes mellitus has been associated with a worsened outcome of influenza**
- **Diabetes tripled the risk of hospitalisation and quadrupled the risk of intensive care unit admission once hospitalized for influenza**
- **Influenza vaccination reduced hospitalisation of working-age persons with diabetes mellitus by 79%**
- **Influenza vaccination was associated with a significant decrease in risk for hospital admission due to stroke, heart failure, and influenza or pneumonia**

M. Goeijenbier et al. / Vaccine 35 (2017) 5095–5101

Influenza and Asthma

- **Asthmatics have more severe influenza symptoms**
- **More complications**
- **More likely to get pneumonia**
- **Annual influenza vaccine strongly recommended**

https://www.cdc.gov/flu/asthma/index.htm

Immunocompromised

- **HIV known immunocompromising condition**
- **About 6 million HIV+; 4 million on no ARV's**
- **HIV known high risk factor for pneumonia**
- **Higher risk of pneumococcal disease even if on ARV's**
- **Known higher risk for influenza**
- Eur J Clin Microbiol Infect Dis (2015) 34:19–31
  DOI 10.1007/s10096-014-2208-6

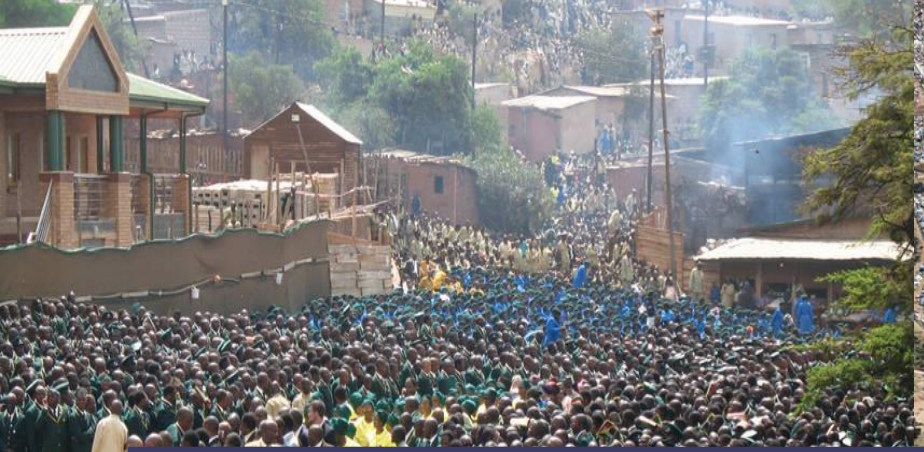
Vaccine Focus Vol 1 No 3 Dec 2014

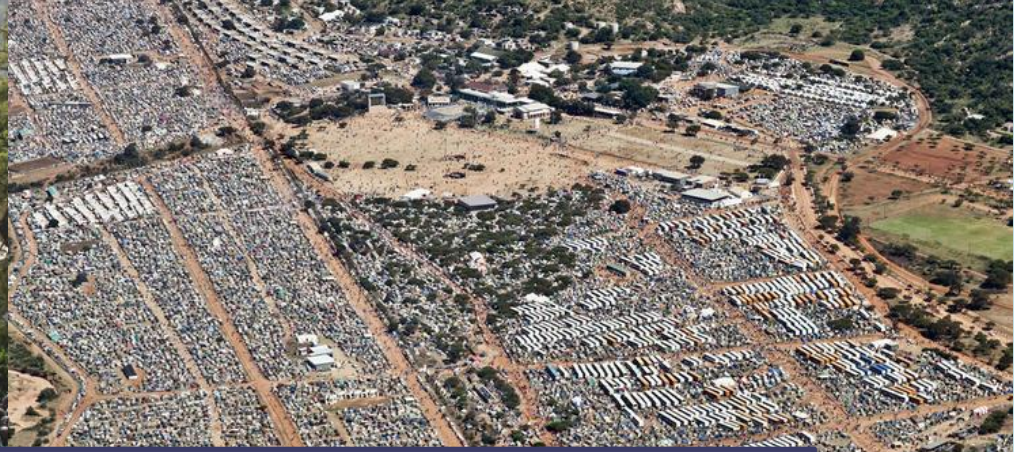
Prevalence Of DVT

Table I. Prevalence of DVT in various patient populations

Patient population	Prevalence of DVT
Internal medicine	10 - 20%
General surgery	15 - 40%
Major gynaecological surgery	15 - 40%
Major urological surgery	15 - 40%
Neurosurgery	15 - 40%
Stroke	15 - 40%
Hip and knee replacement surgery	40 - 60%
Hip fractures	40 - 60%
Polytrauma	40 - 80%
Spinal cord injury	60 - 80%
Critical care	10 - 80%

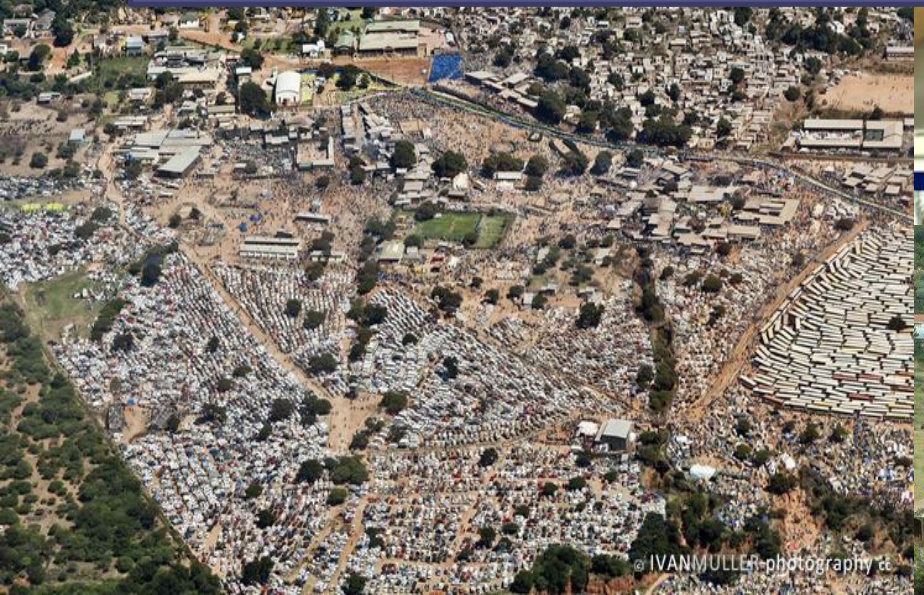
Jacobson et al. *S Afr Med J 2009; 99: 467-473*

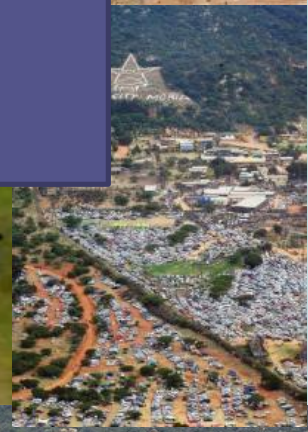




9.5 million flock to Moria this Easter

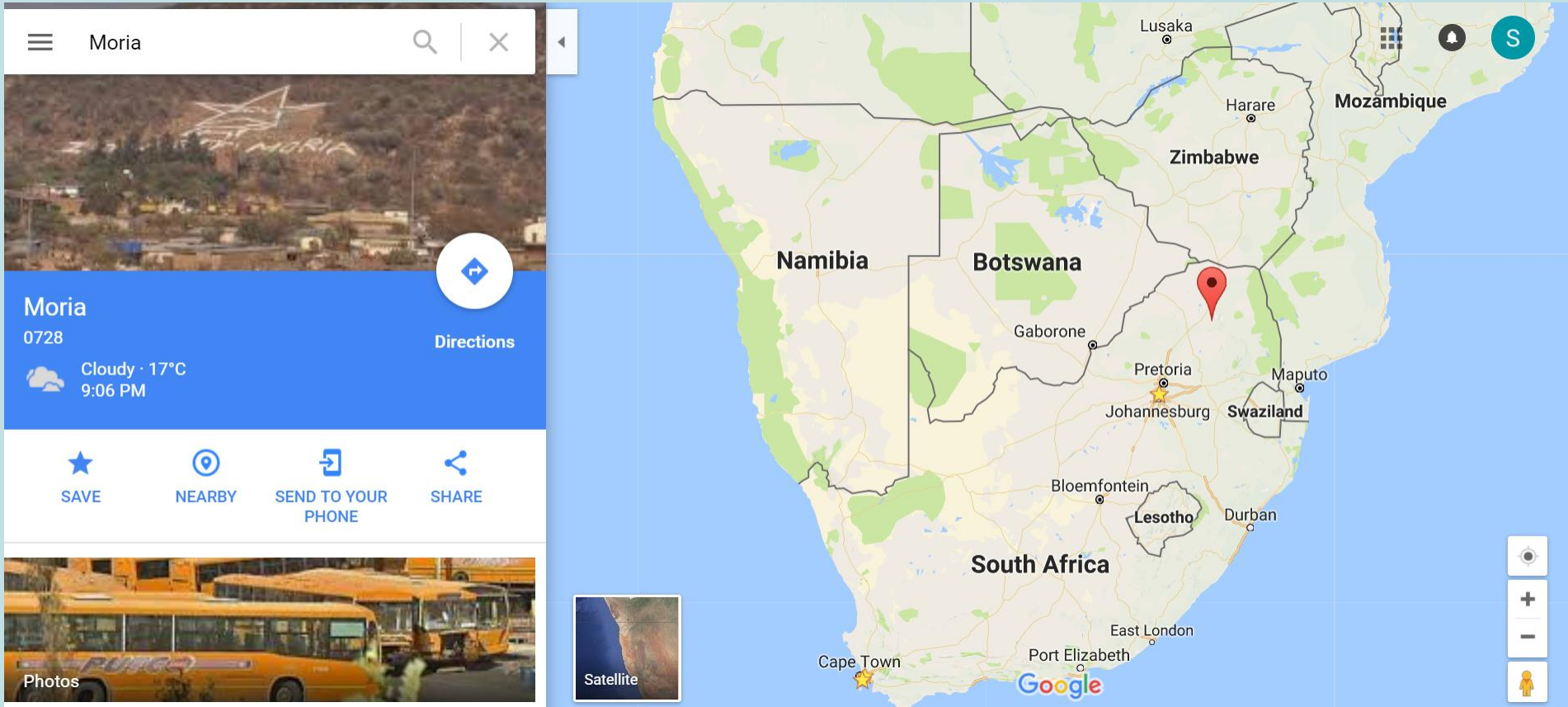
http://www.sanews.gov.za/south-africa/95-million-flock-moria-easter





Moria: Home of Zion Christian Church

Annual Easter (April) Service



Infections acquired by travellers to first world countries

Table 1. Infectious diagnoses, frequency and country acquired

Diagnosis	Frequency (Total=99) and country acquired	
Respiratory	24	
Pneumonia, bacterial (Lobar)	9	6× Australia, Ireland, UK, W. Europe
Influenza (A, B)	6	3× Australia/NZ, 2× USA, Greece
Respiratory tract infection (upper)	5	2× Australia, 2× USA, Switzerland
Atypical pneumonia (diffuse)	1	Australia
Pulmonary *Mycobacterium tuberculosis*	1	UK
Extrapulmonary *Mycobacterium tuberculosis*	1	UK
Acute otitis media	1	Switzerland
Gastrointestinal	24	
Acute diarrhea, bacterial	5	3× Australia, W. Europe, E. Europe
Acute Hepatitis A	2	Australia, NZ
Chronic diarrhea, presumed infectious	3	2× Australia, NZ
Gastroenteritis	3	2× Australia, Bosnia and Herzegovenia
Dientameba fragilis	2	Australia, NZ
Giardia	2	Germany, Greece
Intestinal strongyloides	2	Australia, Bosnia and Herzegovenia

JTM, 2016, 1–4 doi: 10.1093/jtm/taw053

Risk factors for influenza complications

- Children <5, esp less than 2
- Adults > 65
- Pregnancy
- Cardiac disease, diabetes, asthma, obesity
- COPD, liver and renal disease
- Immunocompromised such as HIV+
- Institutionalised people
- Neurological impairment

Influenza/Pneumonia

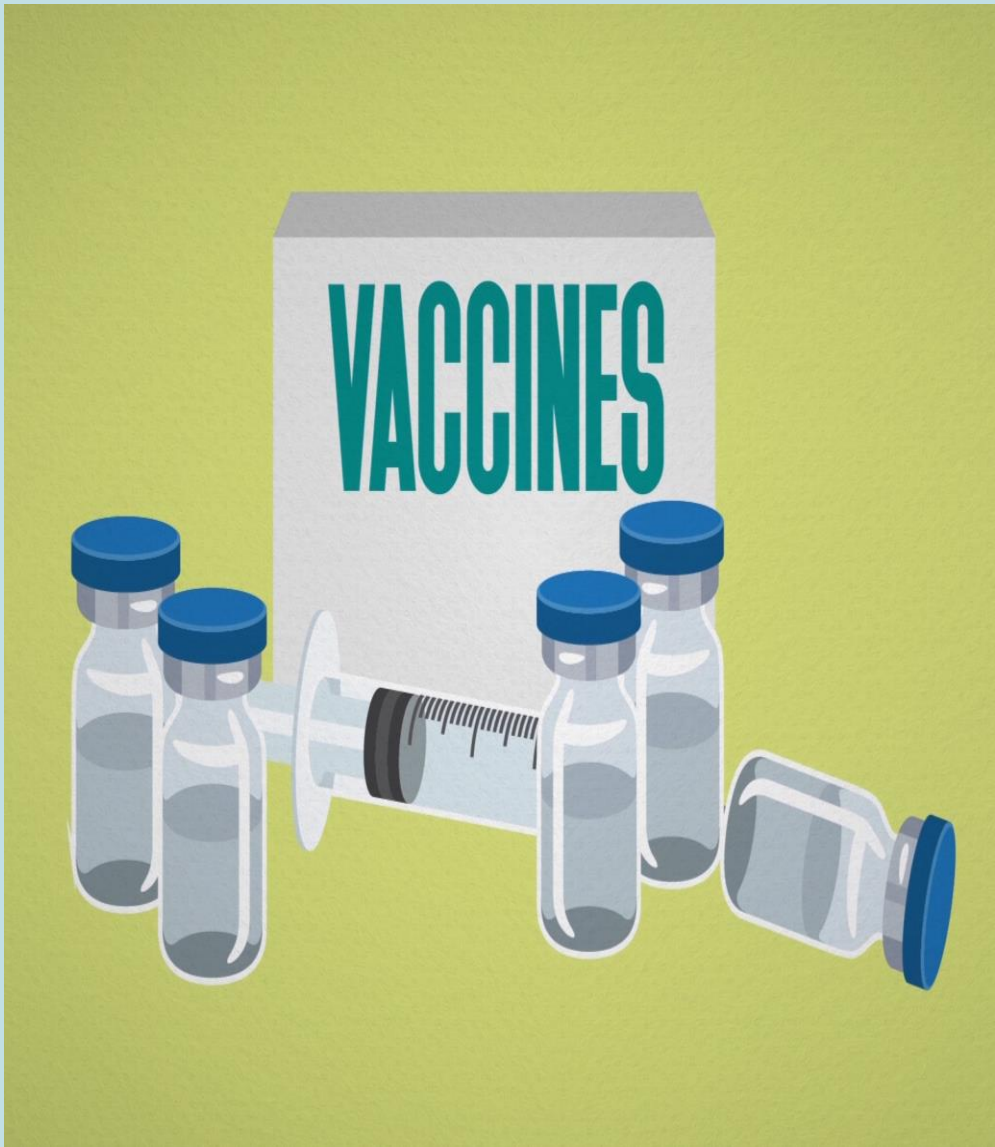
- **Influenza: only predictable aspect is its unpredictability- antigenic drift and shift**
- **Not always able to protect vulnerable in times of pandemics (2009 pandemic H1N1)**
- **PCV 13 vaccine led to decrease of influenza related hospital admissions in children**

  mbio.asm.org January/February 2011 Volume 2 Issue 1 e00309-10 Published by mbio.asm.org
- **Influenza vaccine about 60% efficacious**
- **H3N2 drifted significantly in 2014/2015 (3%-28% VE)**
- **100X increase risk of pneumonia post influenza**

  M. Abd El Ghany et al. / International Journal of Infectious Diseases 47 (2016) 29–3732

Influenza/Pneumococcus

A major cause of death in influenza pandemics is secondary bacterial infections, especially those due to Streptococcus pneumonia, and some of these infections can be prevented with pneumococcal vaccination



Clin Infect Dis 2010; 50:175-83;

Current influenza 2018

- **Put in context, the flu outbreak in Ireland has put 1454 people in hospital in the last three weeks, a rate of 30.5 per 100,000 population**
- **72 in ICU and 34 dead in three weeks**
- **Children have done particularly badly this year**

Connor Maguire 26 Jan 2018

Current influenza 2018

- Worse outbreak in USA since 2010
- Children have done particularly badly this year
- 10 kids died week ending 3 February
- Dominant strain is Influenza A H3N2
- Affects children and the elderly mostly

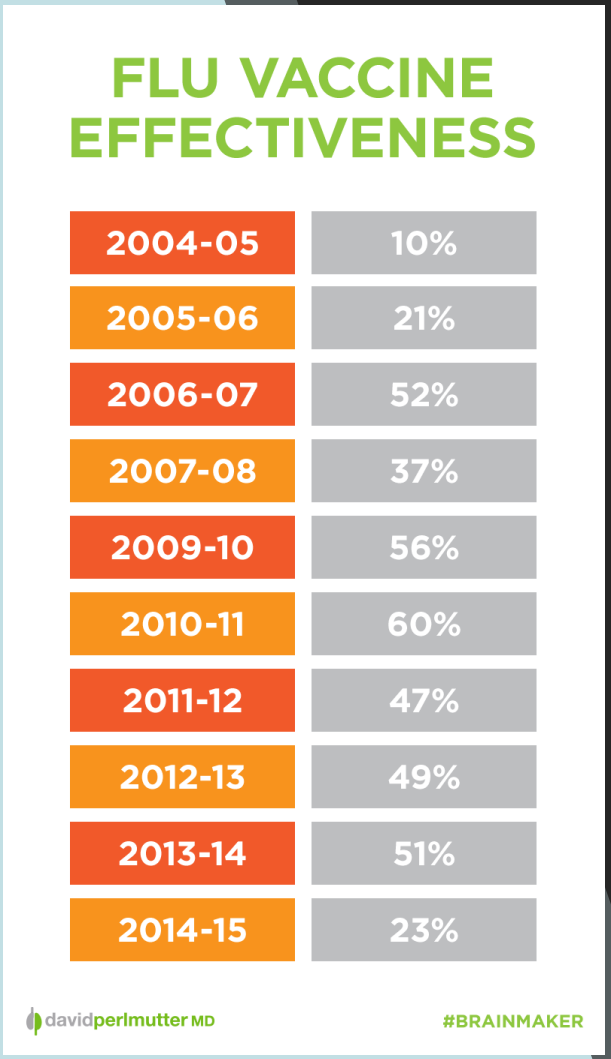
https://www.medicalbrief.co.za/archives/us-flu-outbreaks-worsens-likely-linger-cdc/

Current influenza 2018

- **It knows no international boundaries and kills more people than war or terrorism and this year's [2018] flu outbreak is among the deadliest in a century**
- **The CDC reports over 4000 US deaths a week from flu and pneumonia**
- **In Japan, the 1st week of February saw more than 2.8 million new cases**
- **In Hong Kong, schools were shut for Chinese New Year [16 Feb 2018] early after the outbreak claimed over 120 lives**

http://www.promedmail.org/direct.php?id=20180215.5627287 16 Feb 2018

Efficacy of influenza vaccine



- 48% effective in 2017 (CDC)
- 10% efficacy H3N2 in Australia in 2017
- Influenza B: Victoria and Yamagata
- 2 B strains interchange unpredictably.
- Quadrivalent vaccine containing 2 B strains now to be the way forward

https://blogs.timesofindia.indiatimes.com/voices/flu-vaccine-10-effective/

Composition of 2018 Vaccine

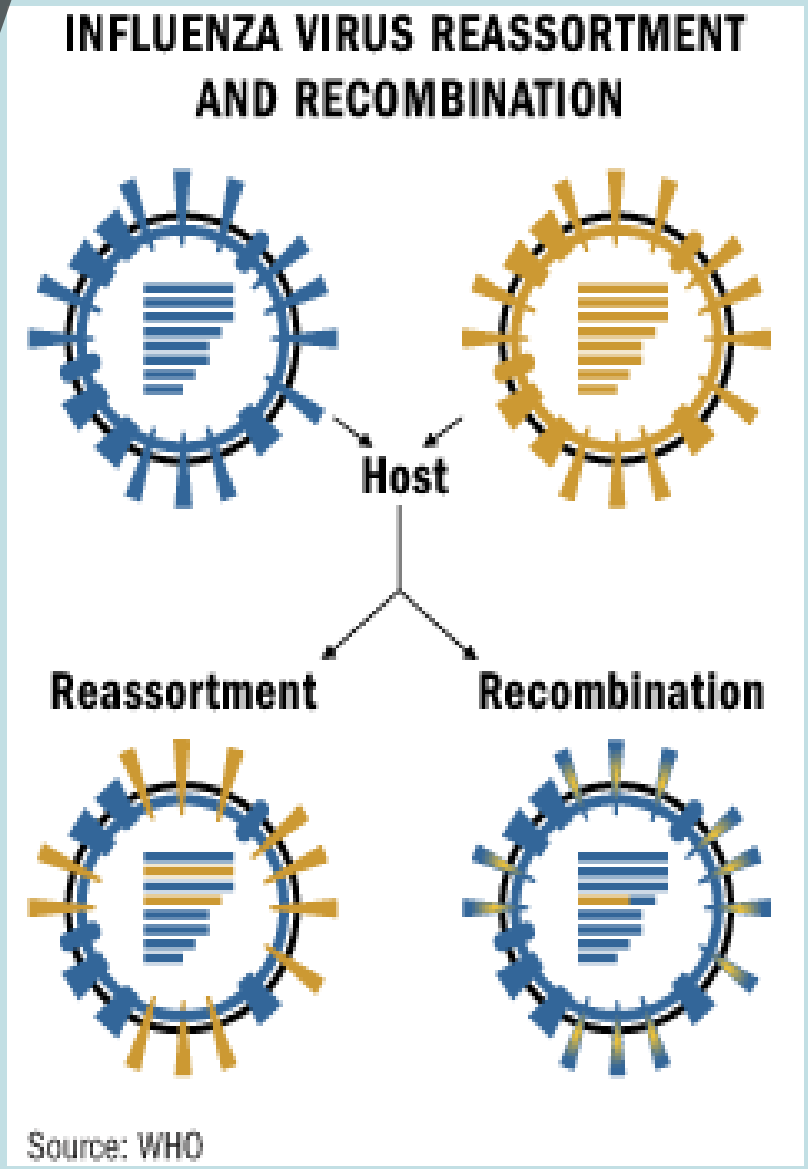
- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
- B/Phuket/3073/2013-like virus (Yamagata)
- It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus
- Good match expected for Southern Hemisphere

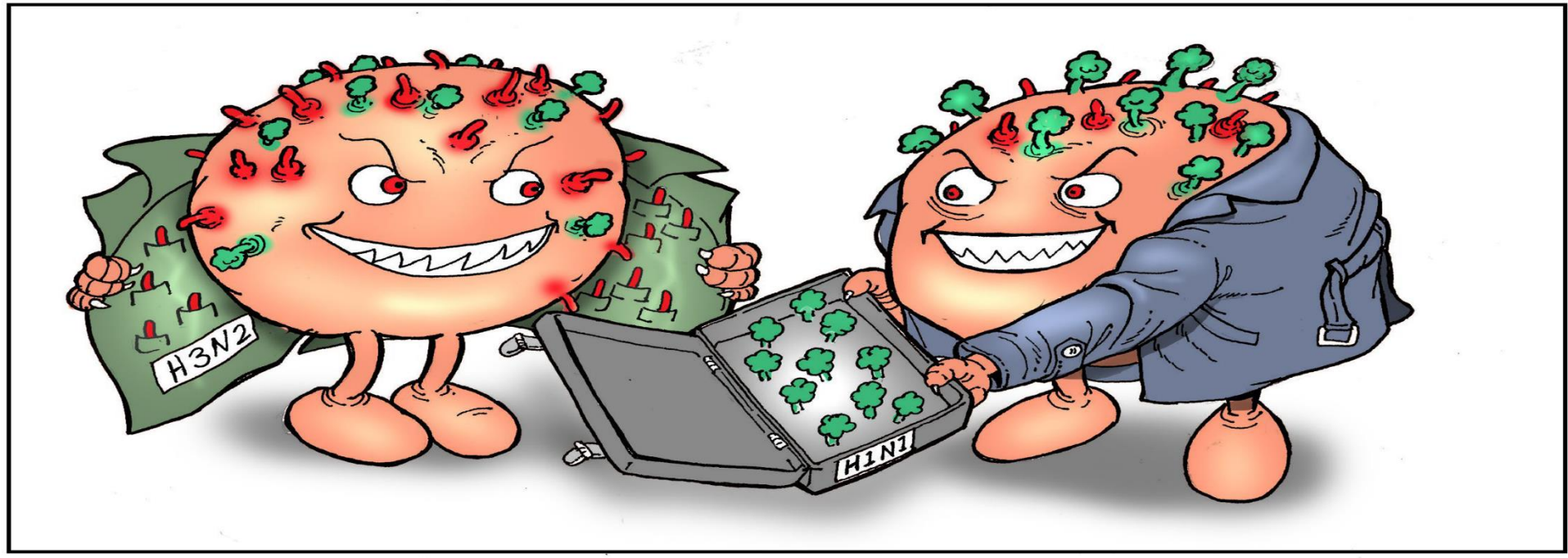
http://www.who.int/influenza/vaccines/virus/recommendations/2018_south/en/

Reassortment

- H1N2 in Netherlands March 2018
- 19 month old child presented with URTI
- 6 gene segments of a seasonal A(H3N2)
- 2 of a seasonal A(H1N1)pdm09

http://www.promedmail.org/direct.php?id=20180322.5702553




H3N2
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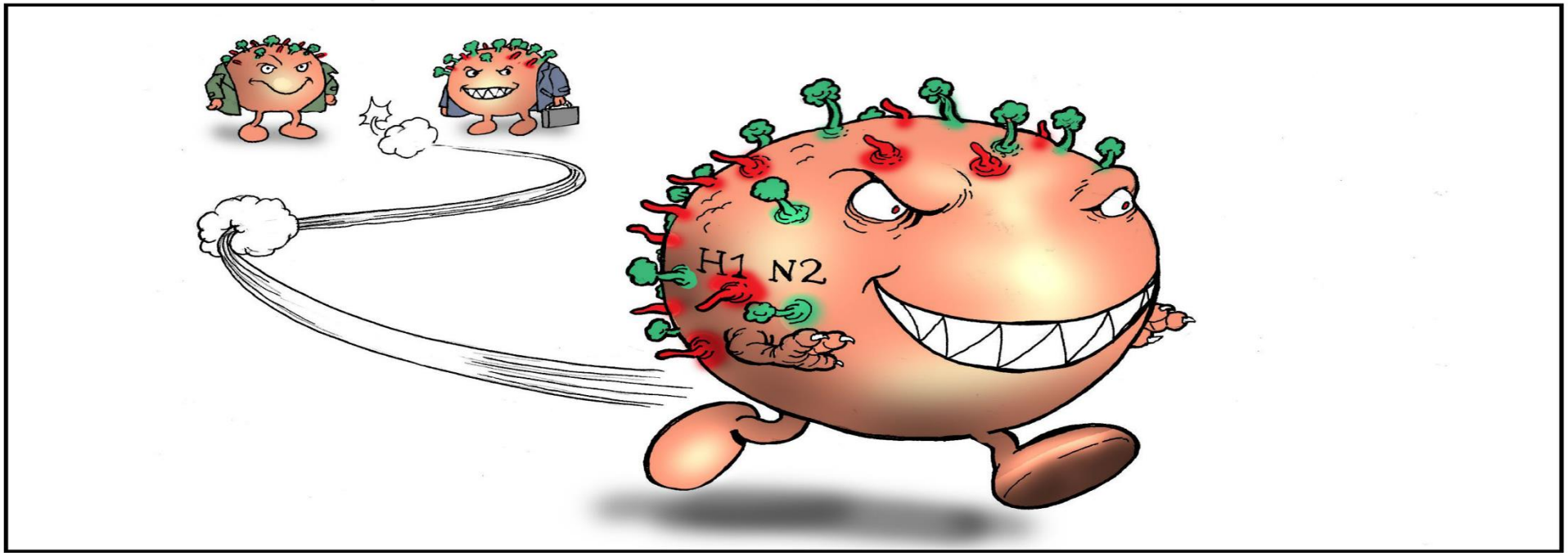
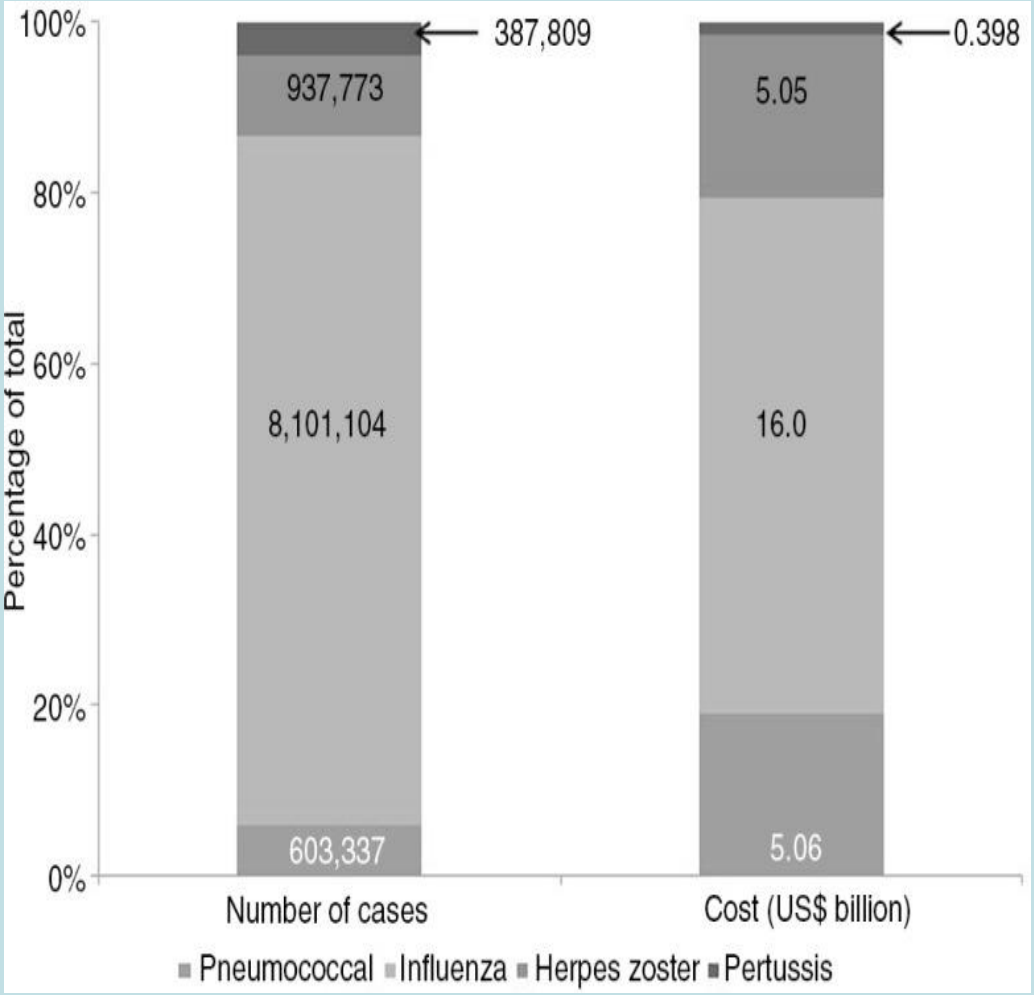

H1
N2

Cost of 4 VPD in 2013 in Adults

- **Adults > 50 in USA**
  - **Influenza (60%)**
  - **Pneumococcus (19%)**
  - **Herpes Zoster (19%)**
  - **Pertussis (2%)**
- **$26.5 billion**
- **Vaccination strongly recommended**



J Prim Prev. 2015 Aug; 36(4):259-73.

Vaccine Preventable Diseases (VPD)

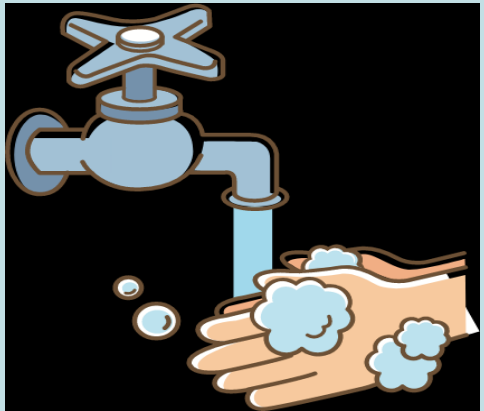
Vaccine-preventable diseases	Age and population at risk of infection	Potential complications and medical impact	lifelong cognitive impairment	lifelong physical impairment	death
Measles	Can be contracted at any age	Pneumonia, encephalitis, death	x	x	x
Chickenpox	90% of cases in children aged <10 years. Fewer than 15% of chickenpox cases in people aged >15 years; most severe cases in adults, with chances of complications increasing with age	Encephalitis, secondary infections (severe streptococcus, skin infection), hepatitis, pneumonia: can be fatal in around 10% of cases	x	x	x
Pneumococcal disease	Any age but most likely to happen in children aged <2 years and adults aged >65 years	Bacterial meningitis, pneumonia, blood infection, septicaemia	x	x	x
Seasonal flu	Can be contracted at any age	Ear and sinus infections, pneumonia, heart inflammation, and death		x	x
Rotavirus gastroenteritis	Mostly in children aged <5 years	Severe dehydration (loss of 10% of weight in children), sometimes death			x
Whooping cough (pertussis)	Can be contracted at any age – most severe cases in babies <6 months of age	Coughing spells so bad that it is hard to eat, drink, or breathe. Can last for weeks and lead to pneumonia, seizures (jerking and staring spells), brain damage, or death	x	x	x

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4802700/table/T0001_27044/

Challenges with influenza prevention

- Virus transmitted by large respiratory droplets
- Minimal benefit from hand hygiene
- Virus shed 24 hrs before symptom onset
- Many adults have asymptomatic infections
- 20-50% of infected HCW asymptomatic
- Infants < 6 months too young to receive vaccine
- Others can't mount protective immune response

Prof S Coffin, CHOP, USA



Sliide from **Angela Dramowski**

Healthcare Workers (HCW)

- **At increased risk for influenza**
- **May transmit it to patients**
- **Vaccinating HCW decreases patient morbidity and mortality in hospitals and long care premises**
- **Decreases HCW absenteeism in USA**
- **Mandatory HCW vaccination practiced in certain places. Ethical?**

http://dx.doi.org/10.1080/21645515.2015.1106656 2017

University Students

- **Campuses: High densities and frequent social interactions**
- **Influenza can spread rapidly**
- **Only 21% of students took vaccine**
- **Of rest:**
  - **48% believed vaccine causes disease**
  - **42% believe vaccine has dangerous S/E**
  - **40% thought they were not at risk**

Influenza Res Treat. 2016; 2016: 4248071.
Published online 2016 Mar
24. doi: 10.1155/2016/4248071

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