Tracking the evolution of avian influenza viruses: are we maximizing the use of the information we have?

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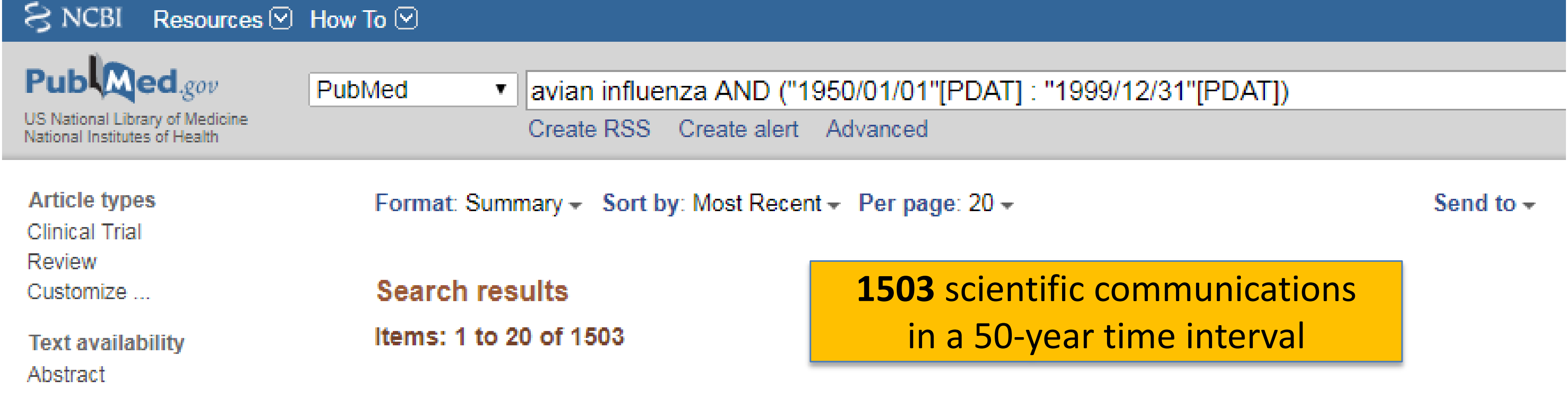
In the framework of the G7 CVOs Meeting
Conference "Avian Influenza. A Global Threat"

Rome, 4th October 2017

The evolution of our awareness of the importance
of AIVs for animal and human health

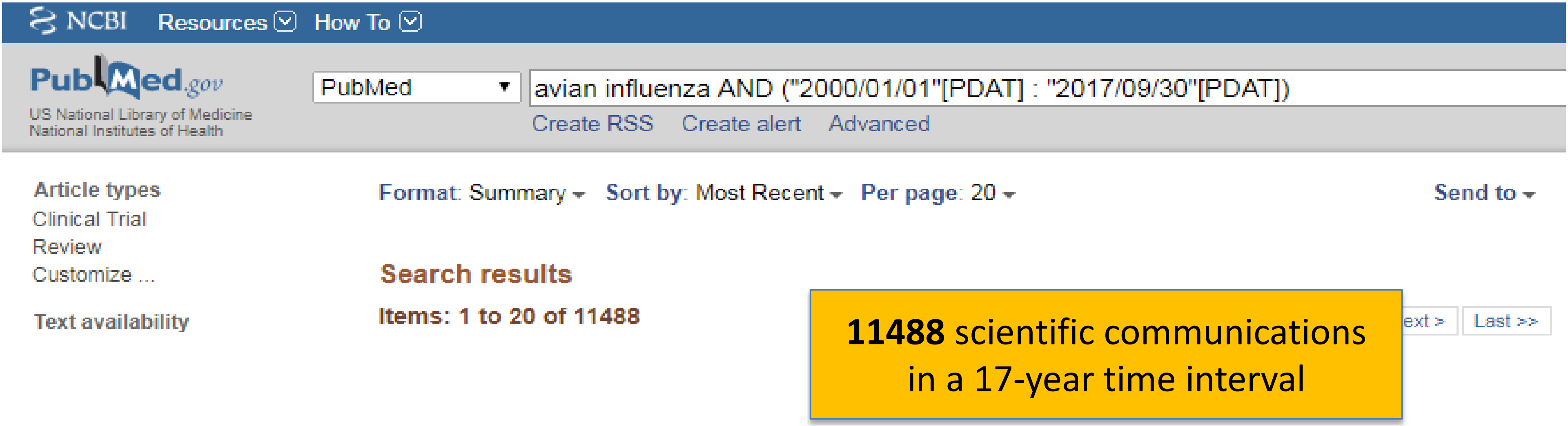


avian influenza AND ("1950/01/01"[PDAT] : "1999/12/31"[PDAT])

Search results

Items: 1 to 20 of 1503

1503 scientific communications in a 50-year time interval

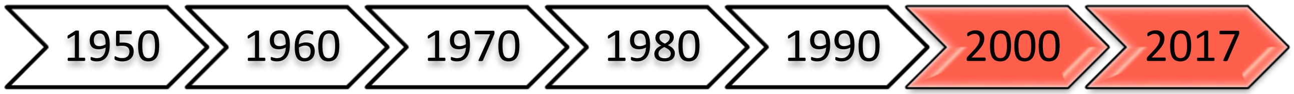


avian influenza AND ("2000/01/01"[PDAT] : "2017/09/30"[PDAT])

Search results

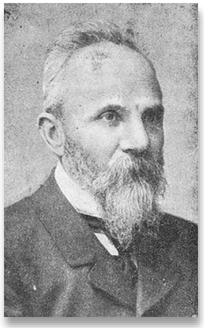
Items: 1 to 20 of 11488

11488 scientific communications in a 17-year time interval



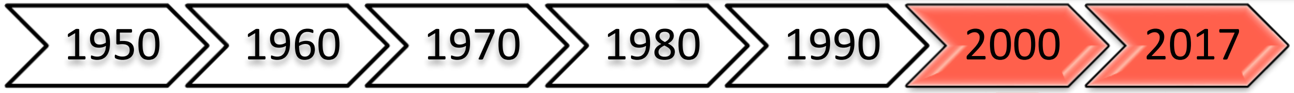
General increase in the number of publications

1503 scientific communications



For over 100 years, HPAI was believed to be a poultry disease of rare occurrence which, in most cases, could cause only a limited number of outbreaks. Minor zoonotic impact

11488 scientific communications

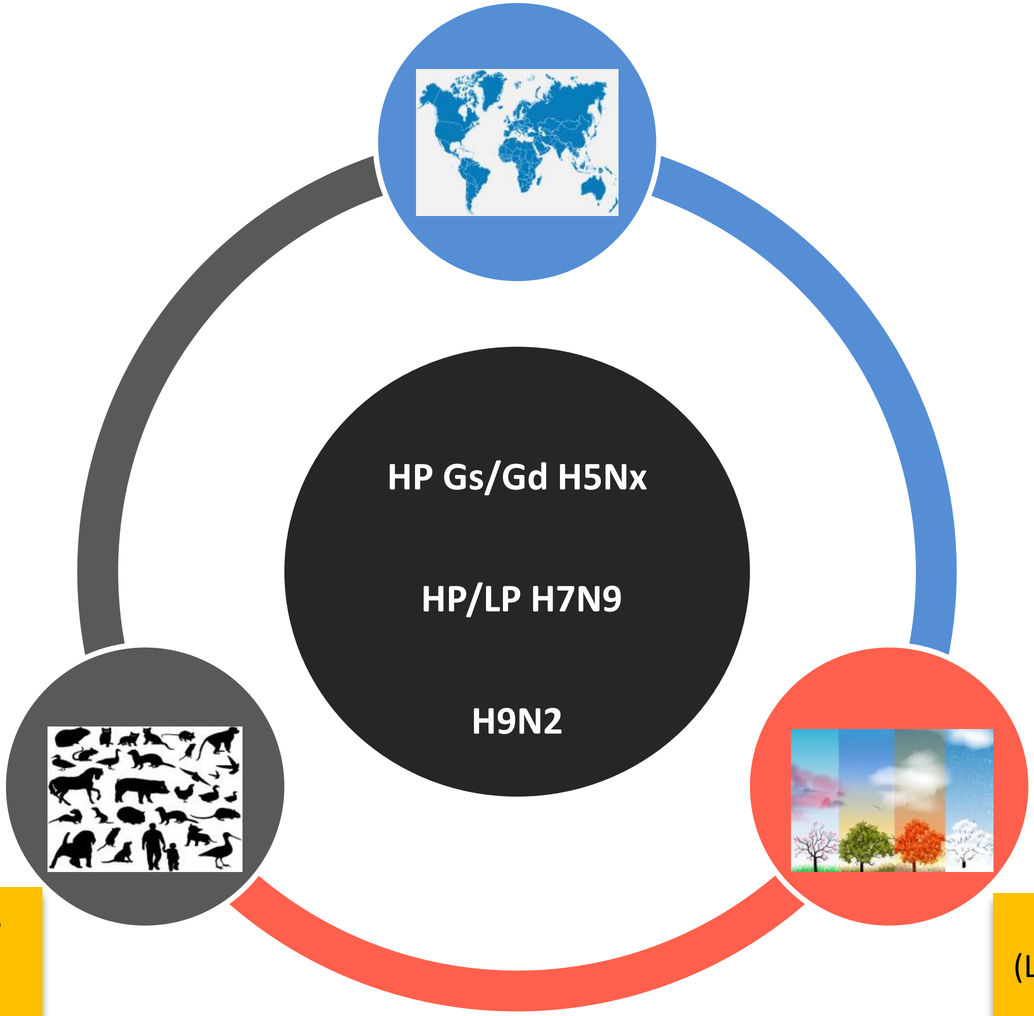


G7 2017
ITALIA

R-Evolution observed in the epidemiological and ecological dynamics of AI

TOP GLOBAL INFECTIOUS DISEASE THREAT

Transcontinental spread most probably through wild birds (H5Nx)
VS
Transcontinental spread most probably through poultry trade (H9N2 G1)



HP Gs/Gd H5Nx

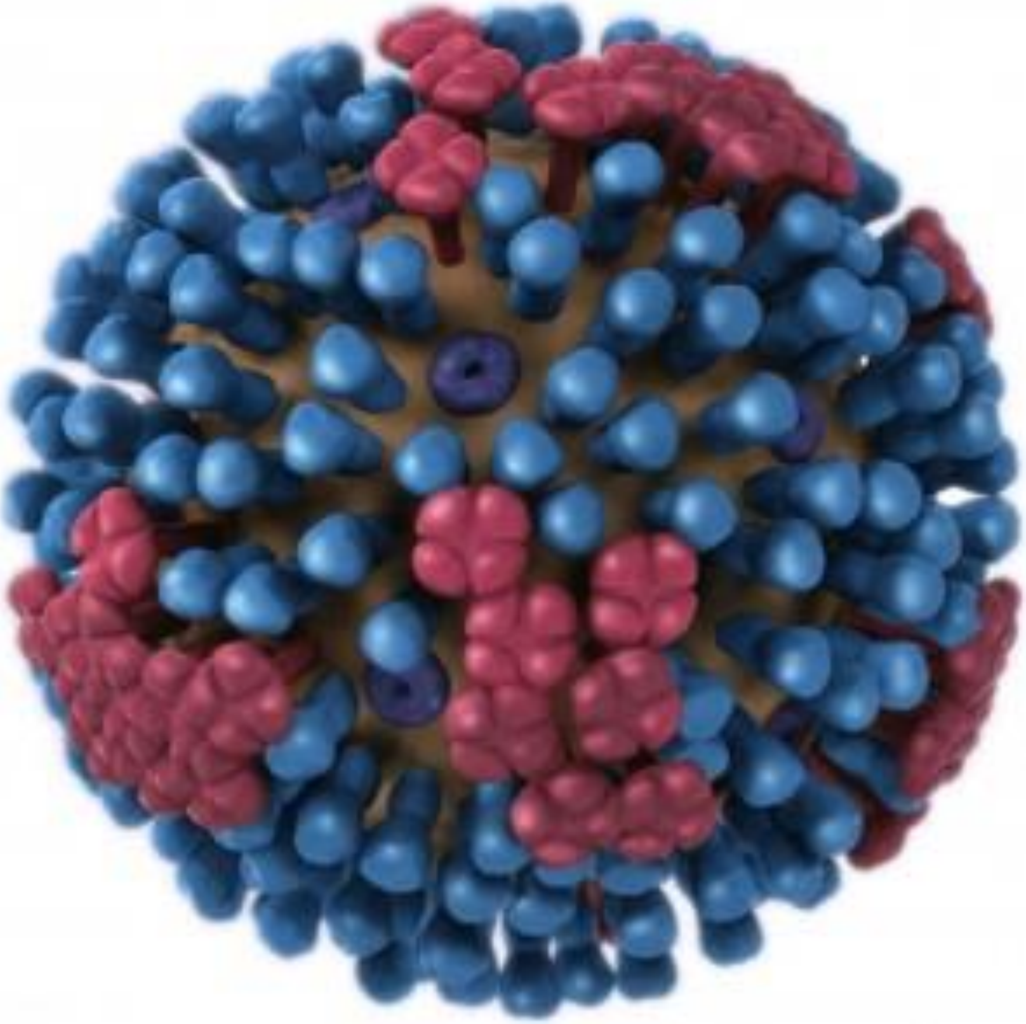
HP/LP H7N9

H9N2

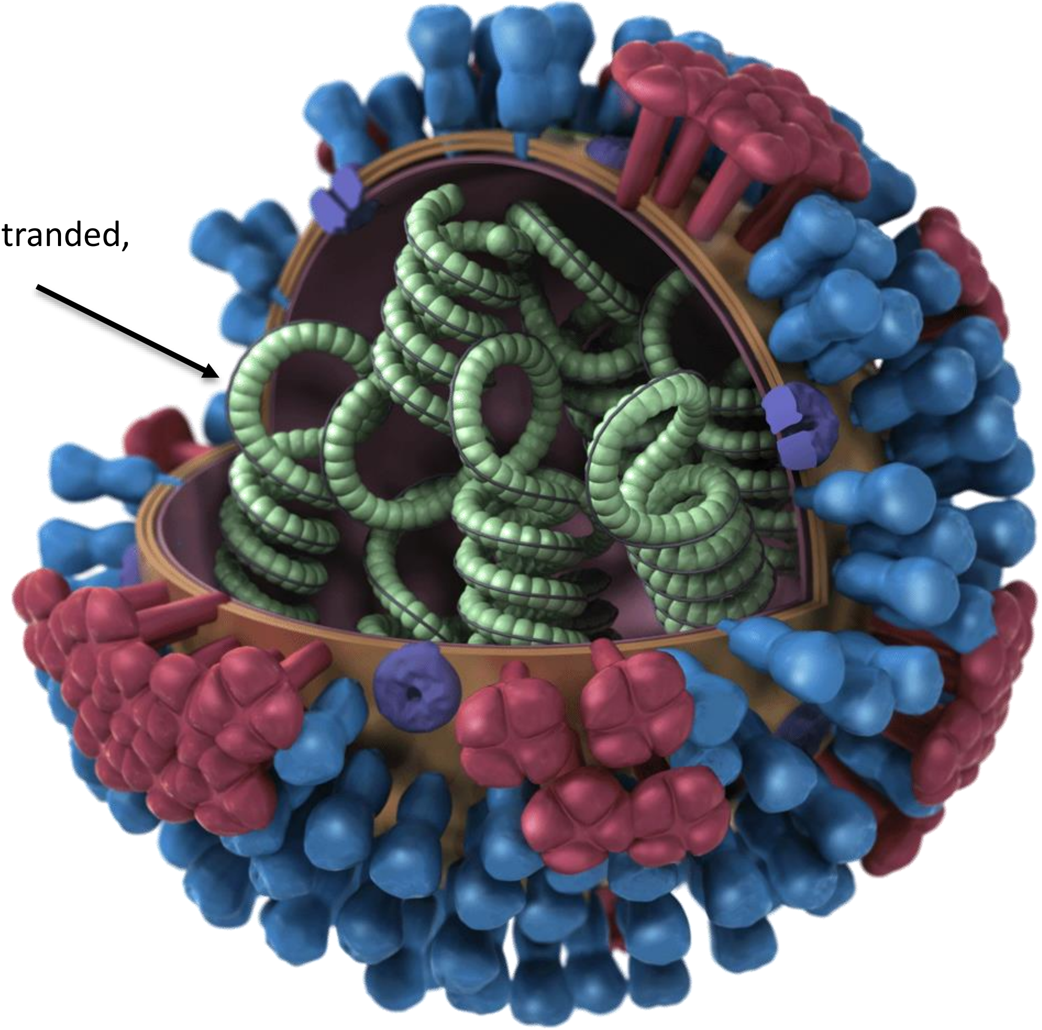
Mild symptoms in humans
(H9N2 G1)
VS
@40% of people confirmed
with Asian H7N9 virus
infection died

Seasonal patterns
(LPAI H7N9 in humans)
VS
Continued
transmission in
poultry (H5Nx)

What is driving the high phenotypic diversity of avian influenza viruses?



http://www.virology.ws

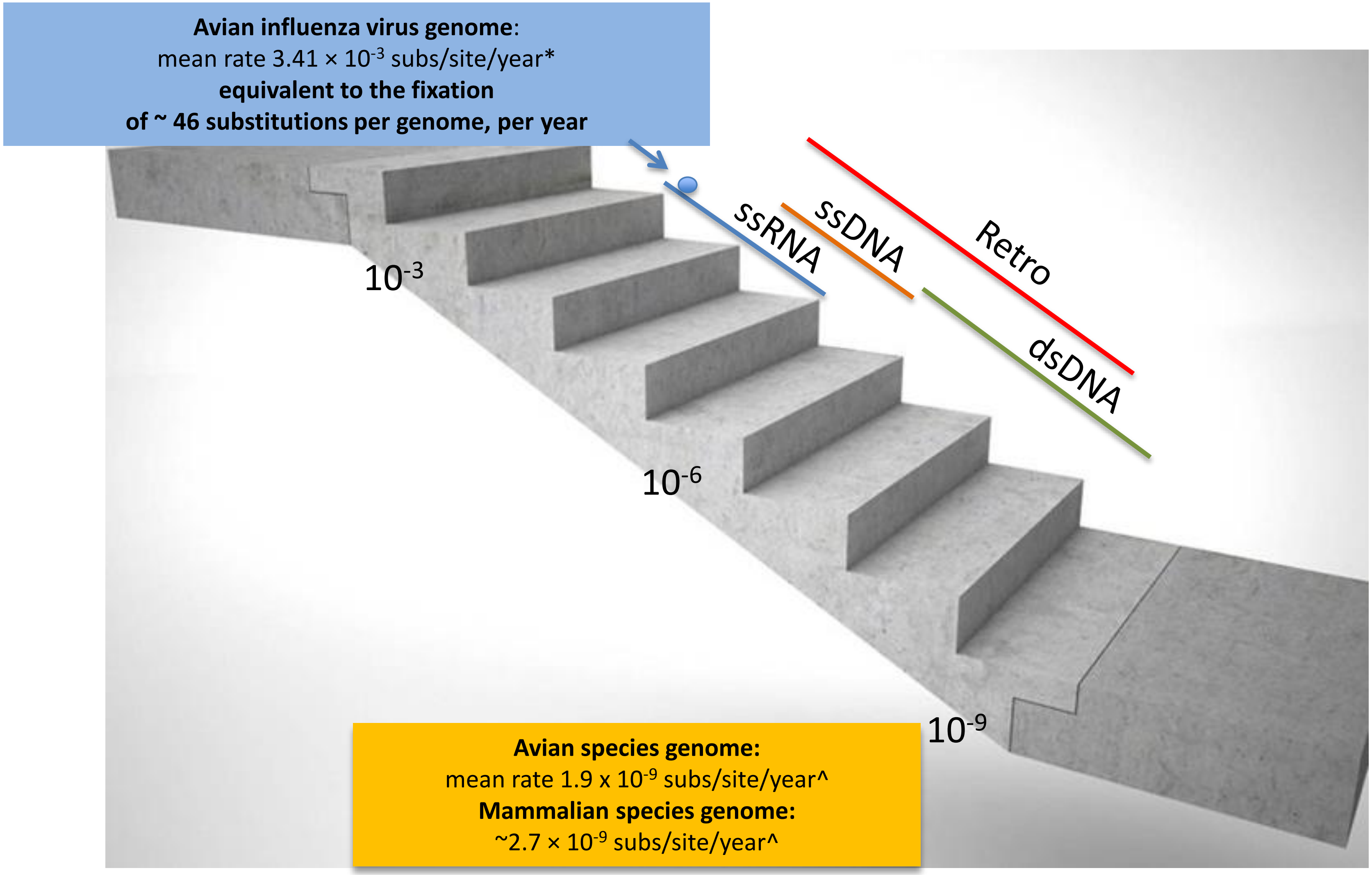


Negative-sense, single-stranded,
segmented RNA virus

http://www.virology.ws

Rapid evolutionary dynamics

High **evolutionary rate** (number of **mutations** that become **fixed in the genome of a population over time)**

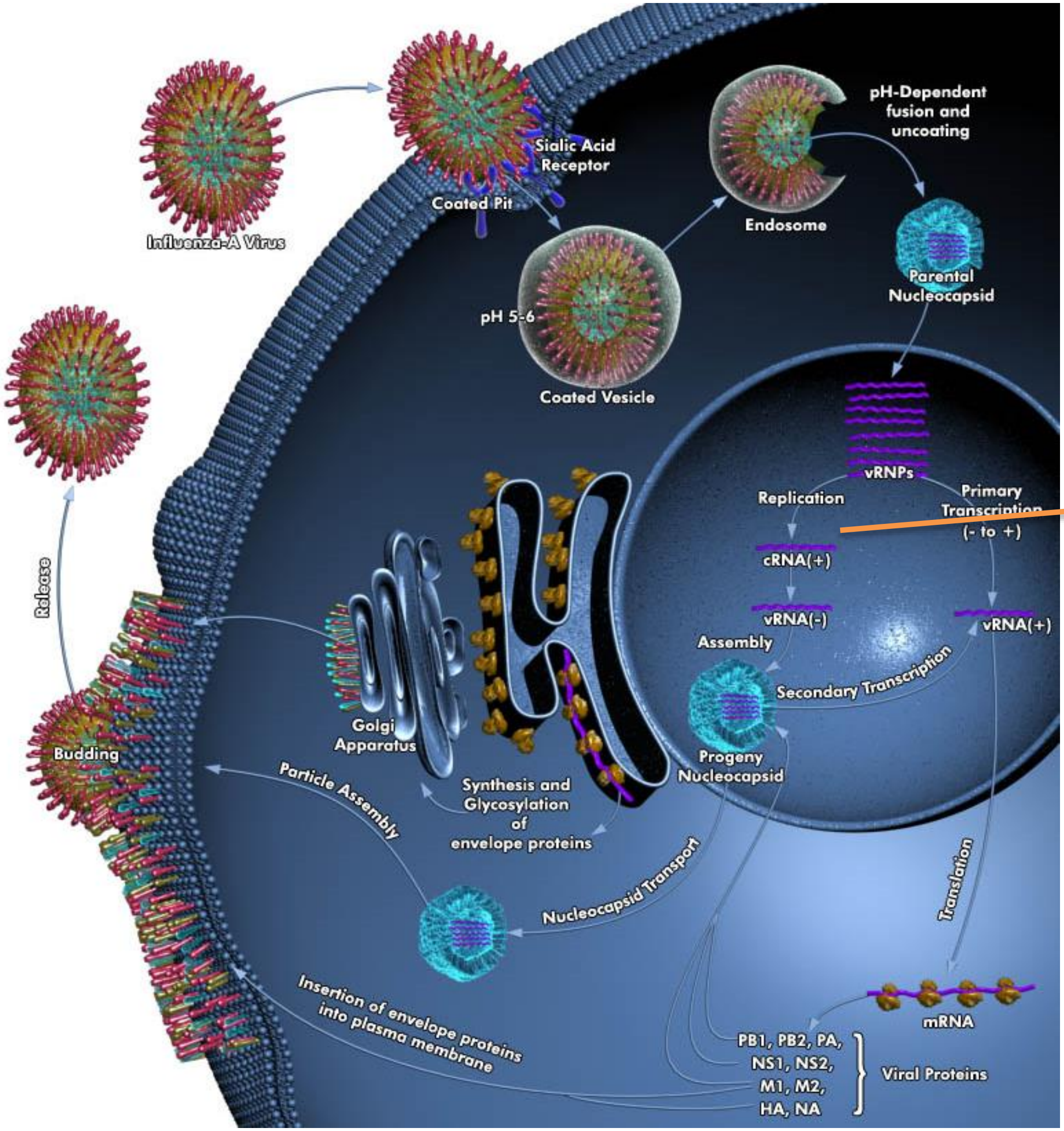


Avian influenza virus genome:
mean rate 3.41 × 10^{-3} subs/site/year*
equivalent to the fixation
of ~ 46 substitutions per genome, per year

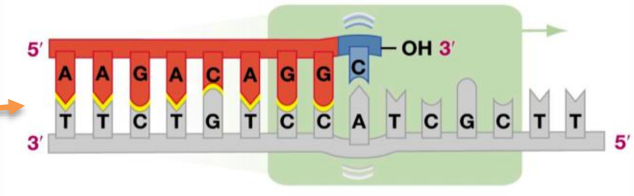
Avian species genome:
mean rate 1.9 x 10^{-9} subs/site/year^
Mammalian species genome:
~2.7 × 10^{-9} subs/site/year^

*Chen and Holmes, 2006 Mol Biol Evol 23(12):2336-2341;
^Zhang et al 2014 *Science.* Science. 2014 Dec 12; 346(6215): 1311–1320

Inherent characteristics predisposing to the observed high evolutionary rate



RNA polymerase is error prone: low fidelity of the polymerases used in replication (**no proofreading capability**)



Viral generation time (replication **speed**)

https://www.qiagen.com/fi/shop/genes-and-pathways/pathway-details/?pwid=247

Selection forces driving the evolution of AI selection

- **Host range**

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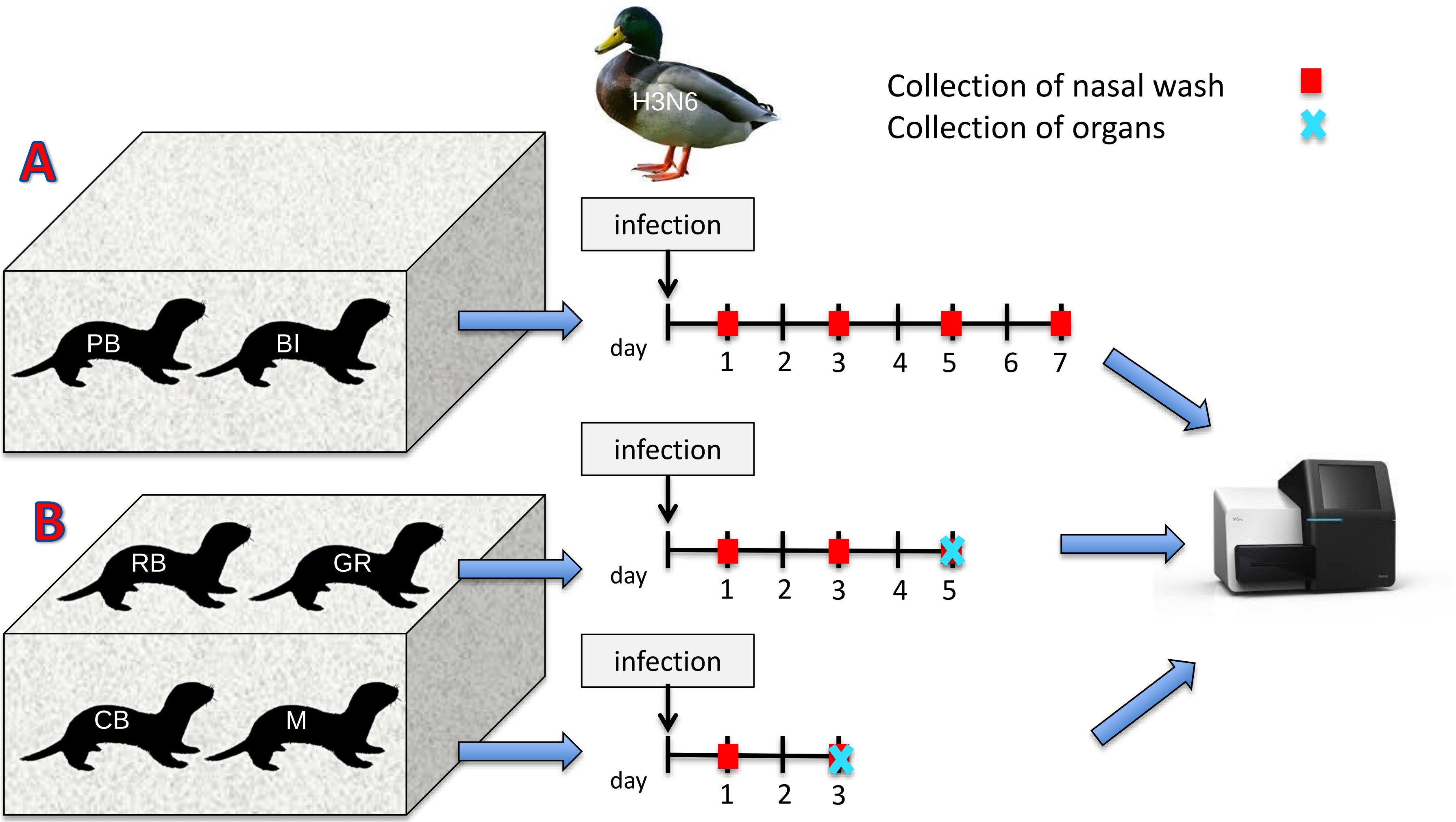
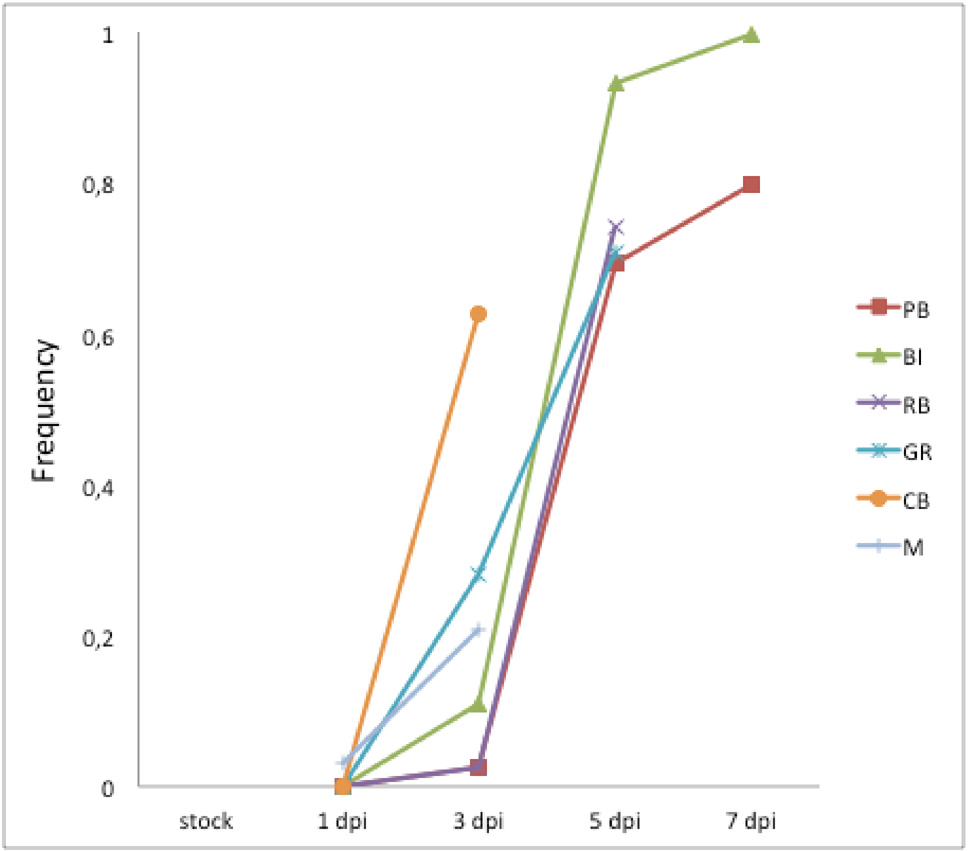


Collection of nasal wash 🟥
Collection of organs ✖

Bonfante et al. 2017 submitted

Avian-to-mammal
adaptation marker (HA gene)

receptor binding specificity
↓ α-2,3 sialic acids
(main receptors of birds)



Since the early stages of virus replication, selective pressure has promoted accumulation of mutations, important for adaptation to mammalian host

Selection forces driving the evolution of AI selection

- Host range
- **Host immunity**

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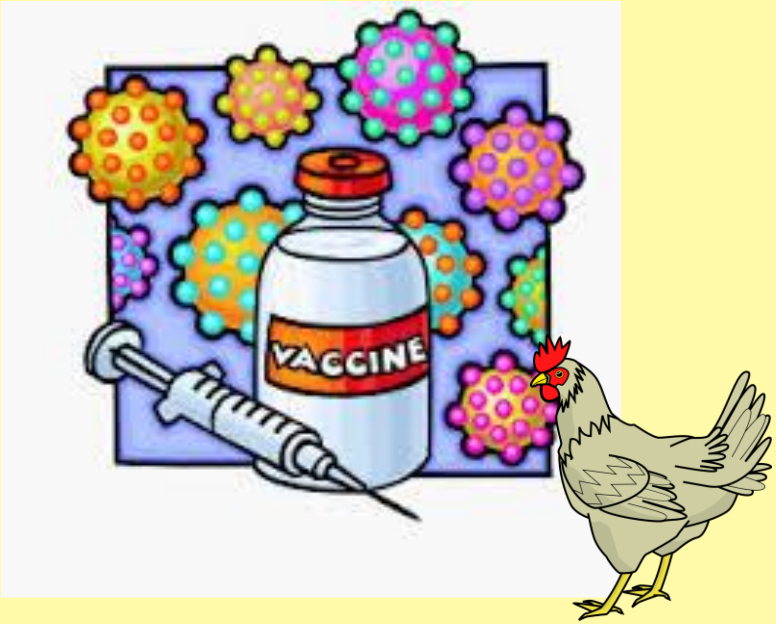
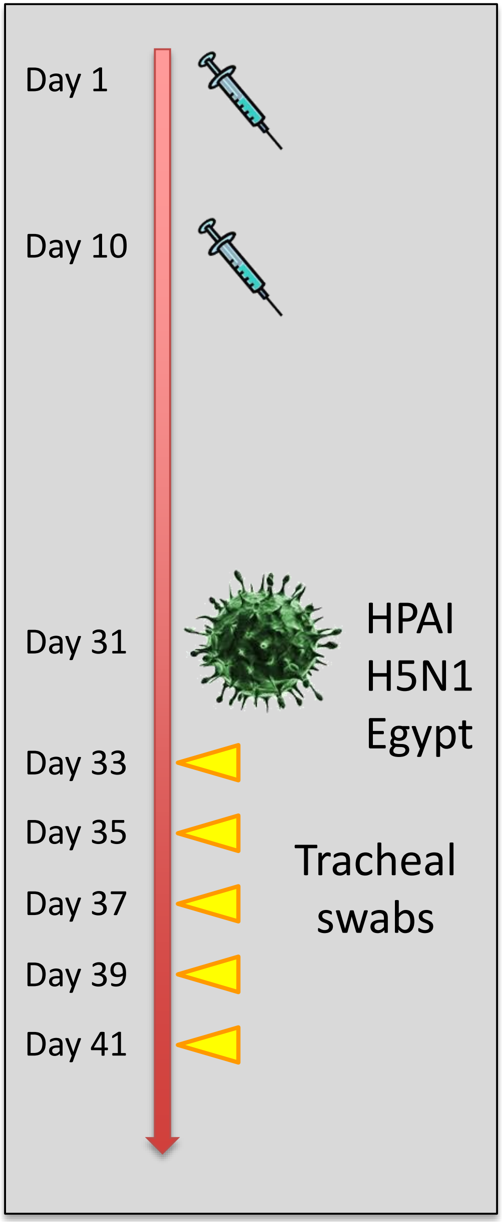
Impact of the vaccine immune pressure on the evolution of avian influenza virus





Day 1

Day 10

Day 31

HPAI
H5N1
Egypt

Day 33

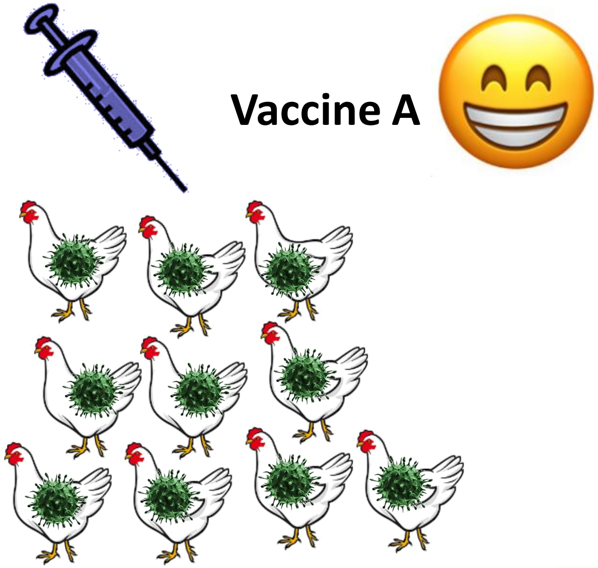
Day 35

Day 37

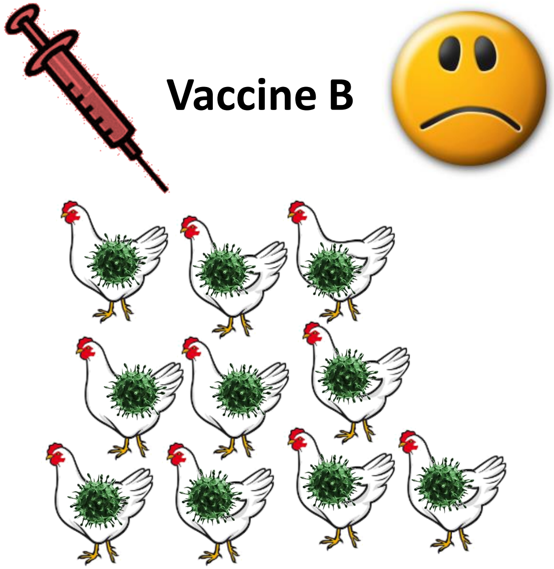
Day 39

Day 41

Tracheal
swabs

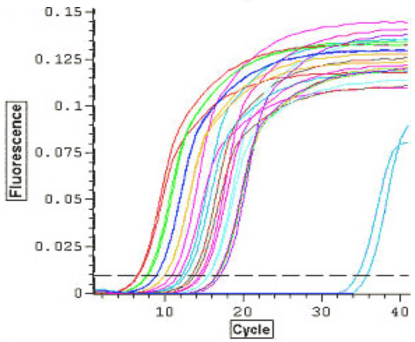


Vaccine A



Vaccine B

Tracheal swabs collected at day 2, 4,
6, 8 and 10 p.i.



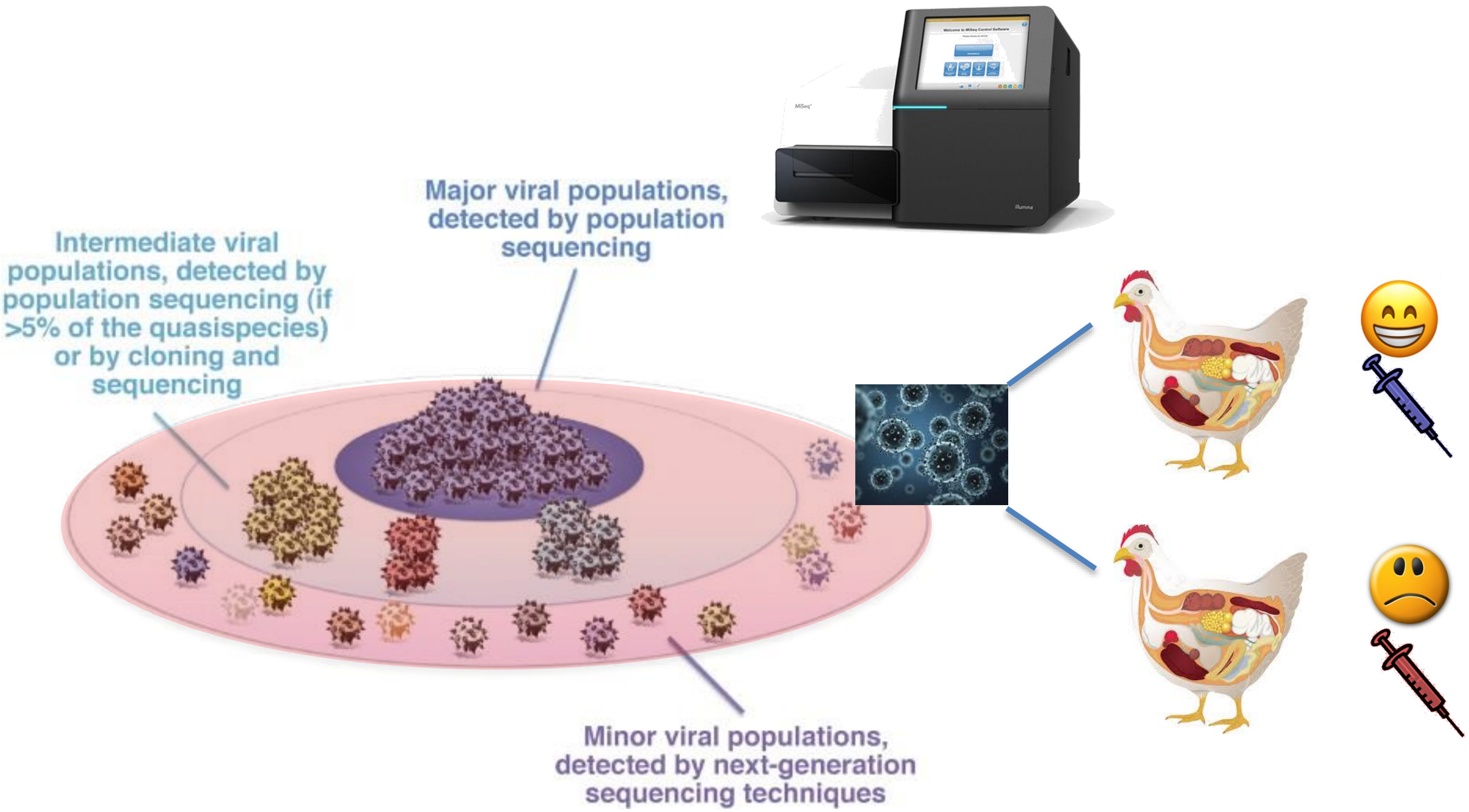
EID50

HA GENE

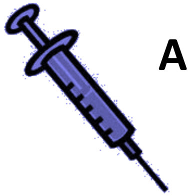
Challenge virus
Group A: 5 samples day 2 p.i.
1 sample day 4 p.i.
Group B: 9 samples day 2 p.i.
5 samples day 4 p.i.

Milani et al. 2017 Vet Mic.

Characterization of the complexity of the viral population



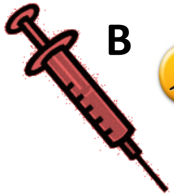
Milani et al. 2017 Vet Mic.



A

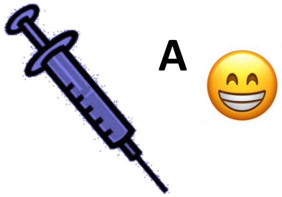
CDS	POLYM	Chall	34A2	35A2	37A2	47A2	59A2	34A4
164	G39E	5,06	0	0	0	0	0	0
229	L61F	0	1,34	0	0	0	0	0
238	N64D	0	1,54	0	0	0	0	0
489	/	0	0	0	0	0	0	1,13
849	/	1,26	0	0	0	0	0	0
1032	/	1,64	0	0	0	0	0	0
1190	V382A	0	0	0	1,12	0	0	0
1222	F393L	0	0	0	0	6,88	0	0
1236	/	0	0	0	0	0	0	2,01
1290	/	1,64	0	0	0	0	0	0
1395	/	1,07	0	0	0	0	0	0
1400	V452A	0	0	0	0	0	0	2,72
1615	/	2,32	0	0	0	0	0	0
1625	L527P	0	0	0	0	0	0	2,35
1701	/	0	0	1,37	0	0	0	0

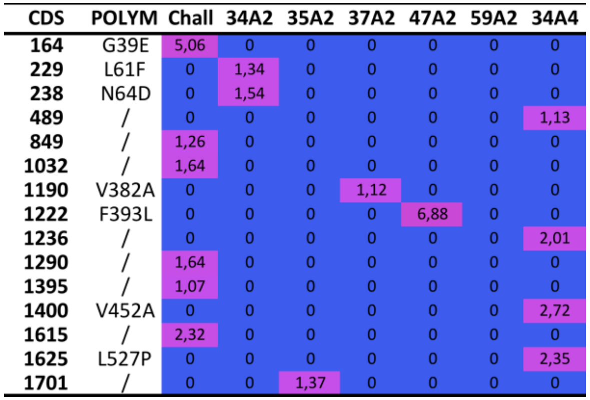
Analysis of genetic polymorphisms



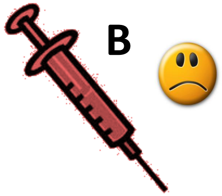
B

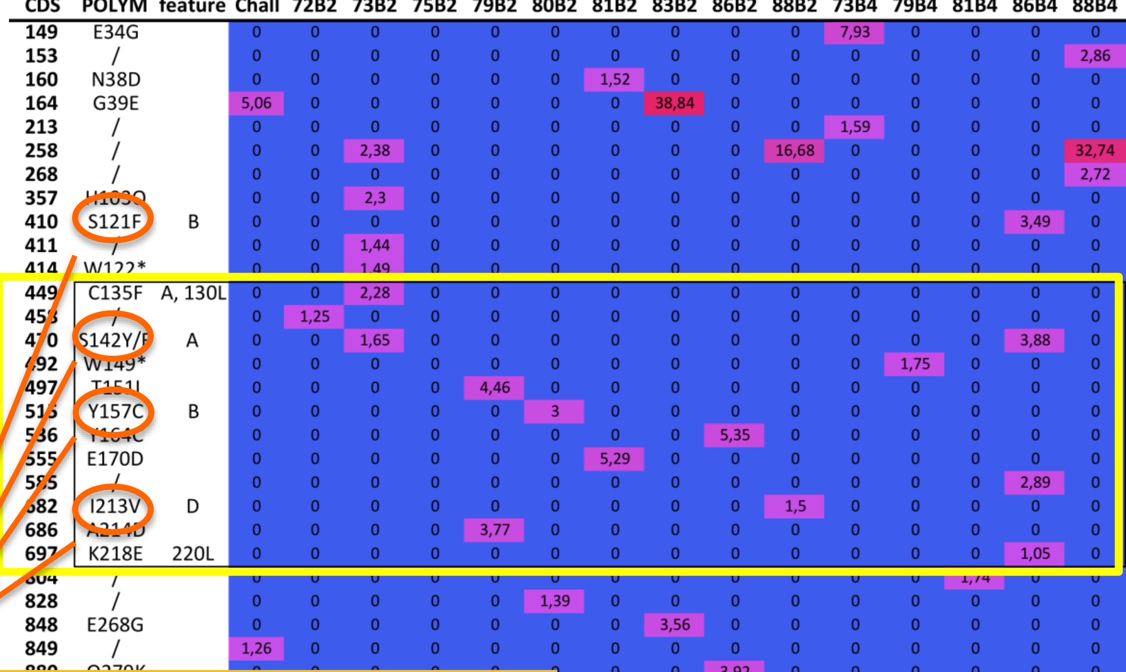
CDS	POLYM	feature	Chall	72B2	73B2	75B2	79B2	80B2	81B2	83B2	86B2	88B2	73B4	79B4	81B4	86B4	88B4
149	E34G		0	0	0	0	0	0	0	0	0	0	7,93	0	0	0	0
153	/		0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,86
160	N38D		0	0	0	0	0	0	1,52	0	0	0	0	0	0	0	0
164	G39E		5,06	0	0	0	0	0	0	38,84	0	0	0	0	0	0	0
213	/		0	0	0	0	0	0	0	0	0	0	1,59	0	0	0	0
258	/		0	0	2,38	0	0	0	0	0	0	16,68	0	0	0	0	32,74
268	/		0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,72
357	H103Q		0	0	2,3	0	0	0	0	0	0	0	0	0	0	0	0
410	S121F	B	0	0	0	0	0	0	0	0	0	0	0	0	0	3,49	0
411	/		0	0	1,44	0	0	0	0	0	0	0	0	0	0	0	0
414	W122*		0	0	1,49	0	0	0	0	0	0	0	0	0	0	0	0
449	C135F	A, 130L	0	0	2,28	0	0	0	0	0	0	0	0	0	0	0	0
458	/		0	1,25	0	0	0	0	0	0	0	0	0	0	0	0	0
470	S142Y/F	A	0	0	1,65	0	0	0	0	0	0	0	0	0	0	3,88	0
492	W149*		0	0	0	0	0	0	0	0	0	0	0	1,75	0	0	0
497	T151I		0	0	0	0	4,46	0	0	0	0	0	0	0	0	0	0
515	Y157C	B	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
536	Y164C		0	0	0	0	0	0	0	0	5,35	0	0	0	0	0	0
555	E170D		0	0	0	0	0	0	5,29	0	0	0	0	0	0	0	0
585	/		0	0	0	0	0	0	0	0	0	0	0	0	0	2,89	0
682	I213V	D	0	0	0	0	0	0	0	0	0	1,5	0	0	0	0	0
686	A214D		0	0	0	0	3,77	0	0	0	0	0	0	0	0	0	0
697	K218E	220L	0	0	0	0	0	0	0	0	0	0	0	0	0	1,05	0
804	/		0	0	0	0	0	0	0	0	0	0	0	0	1,74	0	0
828	/		0	0	0	0	0	1,39	0	0	0	0	0	0	0	0	0
848	E268G		0	0	0	0	0	0	0	3,56	0	0	0	0	0	0	0
849	/		1,26	0	0	0	0	0	0	0	0	0	0	0	0	0	0
880	Q279K		0	0	0	0	0	0	0	0	3,92	0	0	0	0	0	0
931	P296S		0	0	0	0	5,16	0	0	0	0	0	0	0	0	0	0
979	V312I		0	0	1,3	0	0	0	0	0	0	0	0	0	0	0	0
985	A314T		0	0	0	0	0	0	0	0	0	0	0	1,98	0	0	0
1015	E324K		0	0	0	0	0	0	0	2,66	0	0	0	0	0	0	0
1018	R325G		0	0	0	0	0	0	0	0	0	0	0	0	1,44	0	0
1019	R325K		0	0	1,33	0	0	0	0	0	0	0	0	0	0	0	0
1032	/		1,64	0	1,58	68,7	0	54,44	0	0	0	0	6,74	1,25	0	0	15,16
1048	A335T		0	0	1,27	0	0	0	0	0	0	0	0	0	0	0	0
1071	/		0	0	0	0	0	0	0	1,66	0	0	0	0	0	0	0
1107	/		0	0	0	0	0	0	0	0	0	0	0	1,2	0	0	0
1119	N358D		0	0	1,4	0	0	0	0	0	0	0	0	0	0	0	0
1150	E369K		0	0	0	0	10,51	0	0	0	0	0	0	0	0	0	0
1163	K373R		0	0	0	0	0	0	0	0	0	0	0	1,02	0	0	0
1199	I385T		0	0	0	0	0	0	0	0	2,26	0	0	0	0	0	0
1264	I407L		0	0	0	0	0	0	0	0	0	0	0	1,29	0	0	0
1290	/E415D		1,64	0	1,42	0	0	0	0	0	0	0	0	0	0	0	0
1327	L428F		0	0	2,13	0	0	0	0	0	0	0	0	0	0	0	0
1349	E435G		0	0	0	2,92	0	0	0	0	0	0	0	0	0	0	0
1364	F440S		0	0	0	0	0	0	0	0	0	0	0	0	2,71	0	0
1365	/		0	0	0	0	0	0	0	0	0	0	0	1,84	0	0	0
1379	V445A		0	0	0	0	5,67	0	1,54	0	0	0	0	0	0	0	0
1394	D450G		0	0	0	0	0	0	0	3,96	0	0	0	0	0	0	0
1395	/		1,07	0	0	0	0	0	0	0	0	0	6,62	0	0	0	0
1429	E462K		0	0	0	0	0	0	0	0	0	0	0	1,61	0	0	0
1504	Y487H		0	0	0	0	0	0	1,22	0	0	0	0	0	0	0	0
1517	Q491L		0	0	0	0	2,5	0	0	0	0	0	0	0	0	0	0
1522	S493P		0	2,53	0	0	0	0	0	0	0	0	0	0	0	0	0
1575	/		0	0	0	0	0	0	0	0	0	0	0	0	0	2,67	0
1598	S518*		0	0	0	0	0	0	0	0	0	0	0	1,05	0	0	0
1615	/		2,32	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1628	A528V		0	0	0	0	0	0	0	0	0	1,25	0	0	0	0	0





CDS	POLYM	Chall	34A2	35A2	37A2	47A2	59A2	34A4
164	G39E	5,06	0	0	0	0	0	0
229	L61F	0	1,34	0	0	0	0	0
238	N64D	0	1,54	0	0	0	0	0
489	/	0	0	0	0	0	0	1,13
849	/	1,26	0	0	0	0	0	0
1032	/	1,64	0	0	0	0	0	0
1190	V382A	0	0	0	1,12	0	0	0
1222	F393L	0	0	0	0	6,88	0	0
1236	/	0	0	0	0	0	0	2,01
1290	/	1,64	0	0	0	0	0	0
1395	/	1,07	0	0	0	0	0	0
1400	V452A	0	0	0	0	0	0	2,72
1615	/	2,32	0	0	0	0	0	0
1625	L527P	0	0	0	0	0	0	2,35
1701	/	0	0	1,37	0	0	0	0



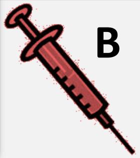


RBD

Ag site

CDS	POLYM	feature	Chall	72B2	73B2	75B2	79B2	80B2	81B2	83B2	86B2	88B2	73B4	79B4	81B4	86B4	88B4
149	E34G		0	0	0	0	0	0	0	0	0	0	7,93	0	0	0	0
153	/		0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,86
160	N38D		0	0	0	0	0	0	1,52	0	0	0	0	0	0	0	0
164	G39E		5,06	0	0	0	0	0	0	38,84	0	0	0	0	0	0	0
213	/		0	0	0	0	0	0	0	0	0	0	1,59	0	0	0	0
258	/		0	0	2,38	0	0	0	0	0	0	16,68	0	0	0	0	32,74
268	/		0	0	0	0	0	0	0	0	0	0	0	0	0	0	2,72
357	H103Q		0	0	2,3	0	0	0	0	0	0	0	0	0	0	0	0
410	S121F	B	0	0	0	0	0	0	0	0	0	0	0	0	0	3,49	0
411	/		0	0	1,44	0	0	0	0	0	0	0	0	0	0	0	0
414	W122*		0	0	1,49	0	0	0	0	0	0	0	0	0	0	0	0
449	C135F	A, 130L	0	0	2,28	0	0	0	0	0	0	0	0	0	0	0	0
453	/		0	1,25	0	0	0	0	0	0	0	0	0	0	0	0	0
470	S142Y/F	A	0	0	1,65	0	0	0	0	0	0	0	0	0	0	3,88	0
492	W149*		0	0	0	0	0	0	0	0	0	0	0	1,75	0	0	0
497	T151I		0	0	0	0	4,46	0	0	0	0	0	0	0	0	0	0
515	Y157C	B	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
536	Y164C		0	0	0	0	0	0	0	0	5,35	0	0	0	0	0	0
555	E170D		0	0	0	0	0	0	5,29	0	0	0	0	0	0	0	0
585	/		0	0	0	0	0	0	0	0	0	0	0	0	0	2,89	0
682	I213V	D	0	0	0	0	0	0	0	0	0	1,5	0	0	0	0	0
686	A214D		0	0	0	0	3,77	0	0	0	0	0	0	0	0	0	0
697	K218E	220L	0	0	0	0	0	0	0	0	0	0	0	0	0	1,05	0
804	/		0	0	0	0	0	0	0	0	0	0	0	0	1,74	0	0
828	/		0	0	0	0	0	1,39	0	0	0	0	0	0	0	0	0
848	E268G		0	0	0	0	0	0	0	3,56	0	0	0	0	0	0	0
849	/		1,26	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Suboptimal immune protection may induce an increase of the complexity in the viral population from the early stages of infection and may promote the selection of minority variants some of which may be **involved in antigenic drift.**



A	B
9 minority variants	64 minority variants + 2 fixed mutation
9 HA positions showing mutations	57 HA positions showing mutations
1 to 4 variants per sample	2 to 13 variants per sample
0 minority variants in the RBD	13 minority variants in the RBD
0 minority variants in the Ag sites	6 minority variants in the Ag sites
0 variants shared between samples	4 variants shared between samples

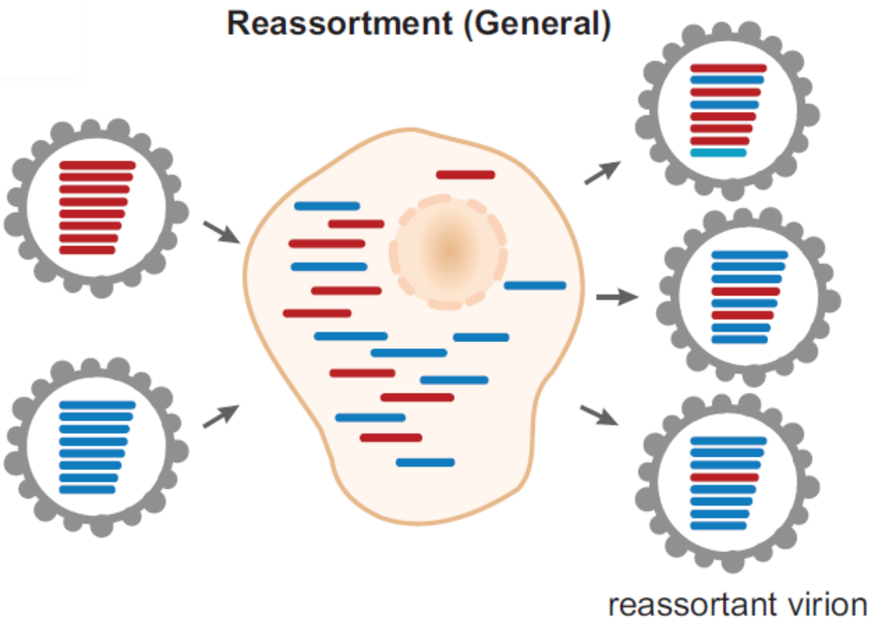
Selection forces driving the evolution of AI selection

- Host range
- Host immunity
- **Eco-environmental factors** (i.e., farm type, land use, population size, control measures such as the use of antiviral treatments)

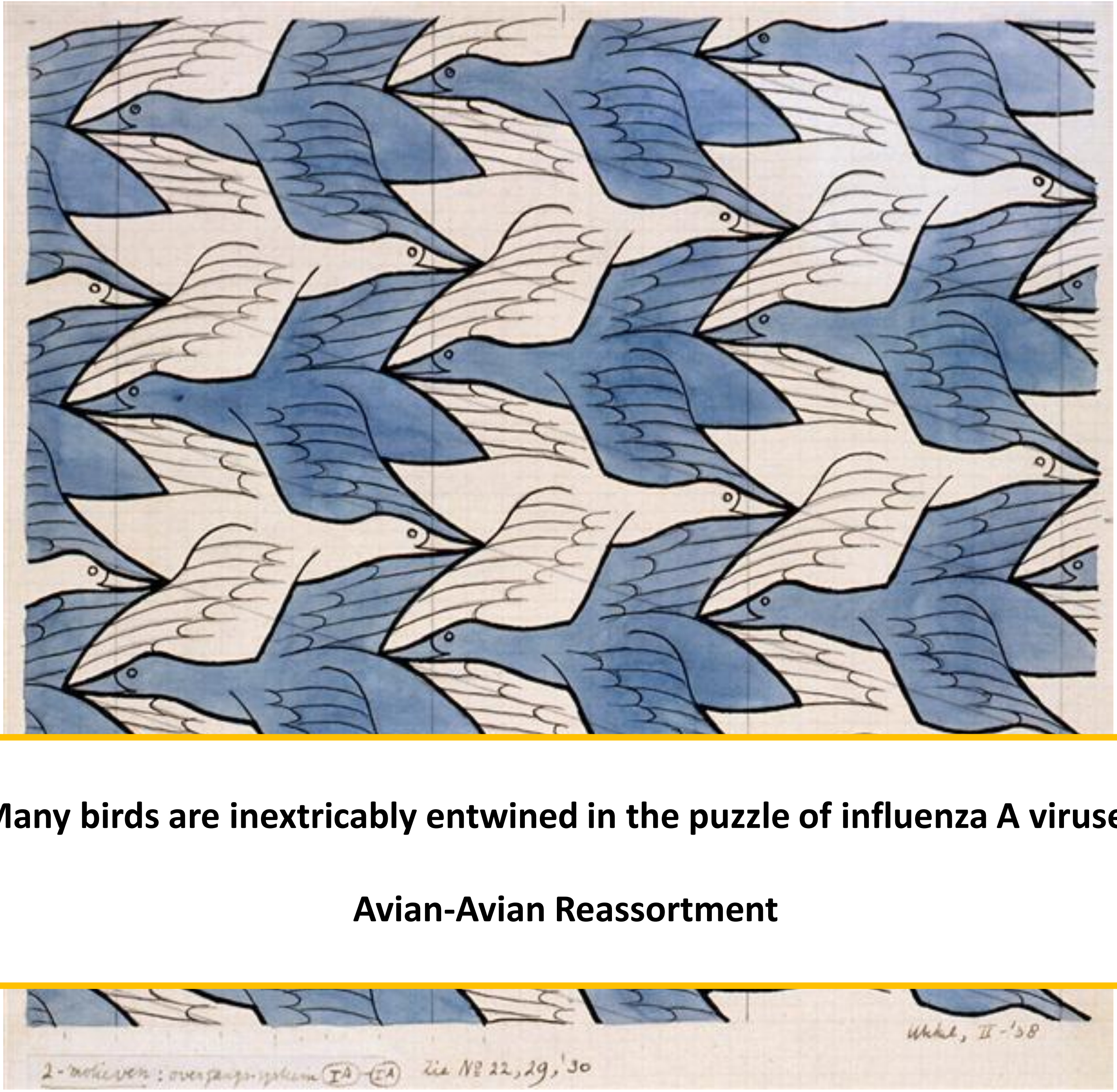
Inherent characteristics predisposing to the high diversity of AI viruses

Genome Structure

8 interchangeable RNA molecules: reassortment has the potential to vastly increase the diversity of circulating influenza viruses



Lam et al. Critical Reviews in Clinical Laboratory Science, 2010; 47(1): 5–49



Many birds are inextricably entwined in the puzzle of influenza A viruses.

Avian-Avian Reassortment

Cornelis Escher, 1938. Two birds

Many species are inextricably entwined in the puzzle of influenza viruses.

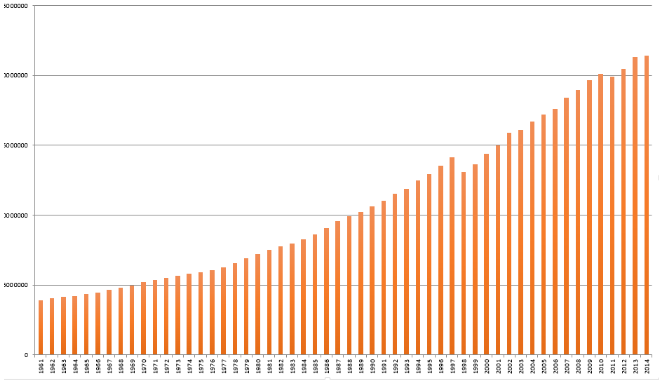
Reassortment Between Avian And Mammalian Viruses

Cornelis Escher, 1957. Litografia. mm. 370 x 315

Virus intrinsic ability to accumulate genetic diversity

+

host populations size



=

- endless variety of new viruses with potentially new properties
- difficulty to control their spread and need for tailored control measures

High mutation rates make evolution of AI happening right in front of our eyes, facilitating the reconstruction of emergence, transmission and spread dynamics thanks to the exploitation of genetic and epidemiological data.

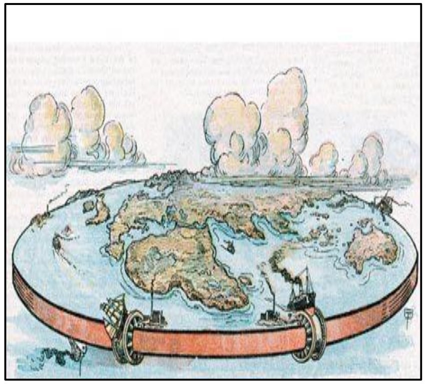
An age of genomic plenty:
Next-generation evolutionary epidemiology

Fast-growing innovations in the field of genetic sequencing technology

Rapid and sustained growth in computer processing power and concomitant advances in methods of statistical inference

What's in our toolbox?

R-Evolution in Sequencing technologies



Discovery of DNA structure by Watson and Crick [**1953**]

First Generation Sequencing

- Maxam-Gilbert sequencing [**1977**]
- Sanger Sequencing [**1977**]
  - Gel-based systems
  - Capillary sequencing [**1998**]

Next (or Second) Generation Sequencing (NGS)

- Massively parallel sequencing [**2005/2006/2007/2011**]
- 454 / Roche sequencing
- Illumina (Solexa) sequencing
- SOLiD systems
- Ion Torrent sequencing

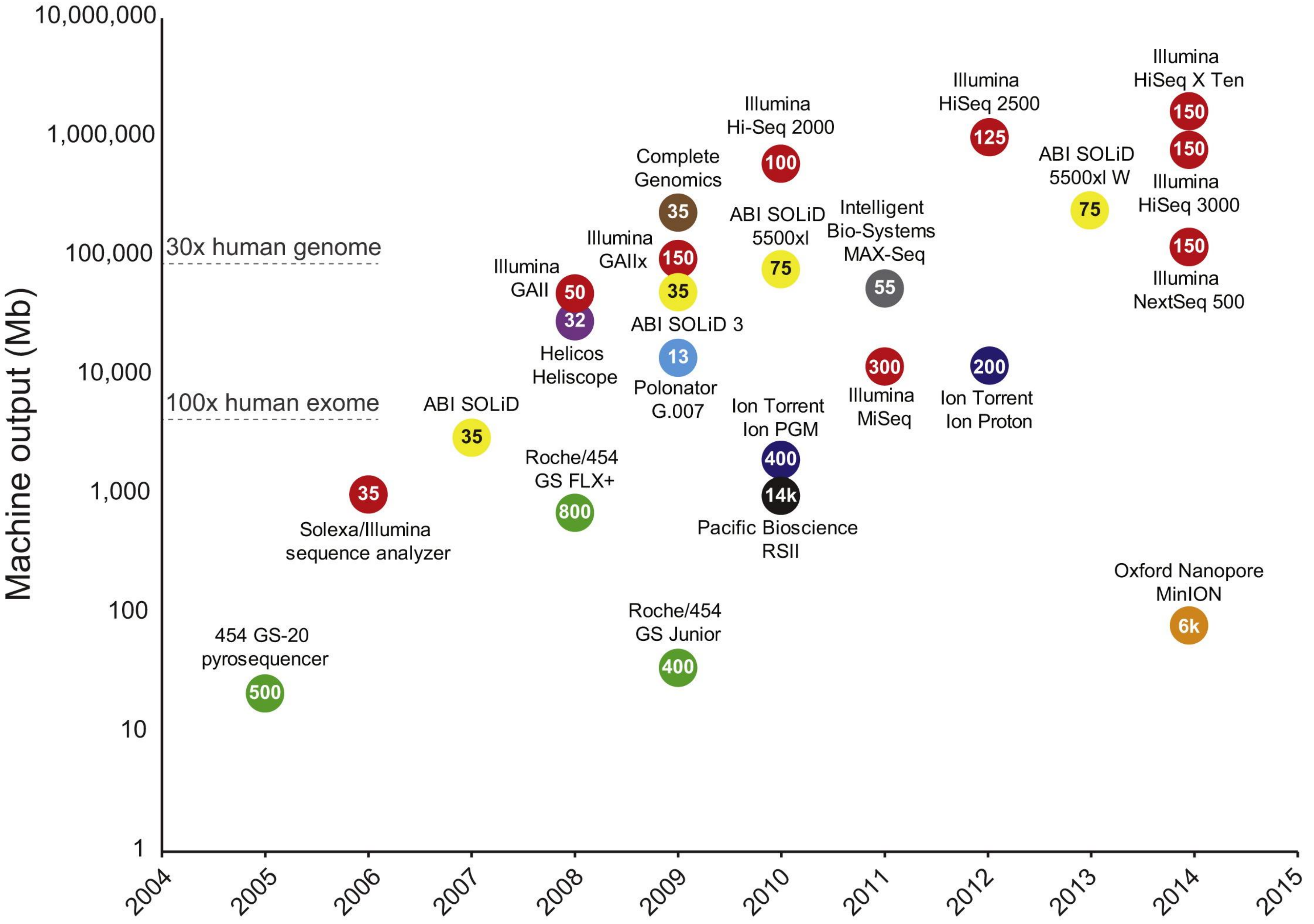
Third Generation Sequencing

- Single molecule sequencing [**2013**]
- PacBio RS II (Pacific Biosciences)
- MinION (Oxford Nanopore)

Fourth generation sequencing

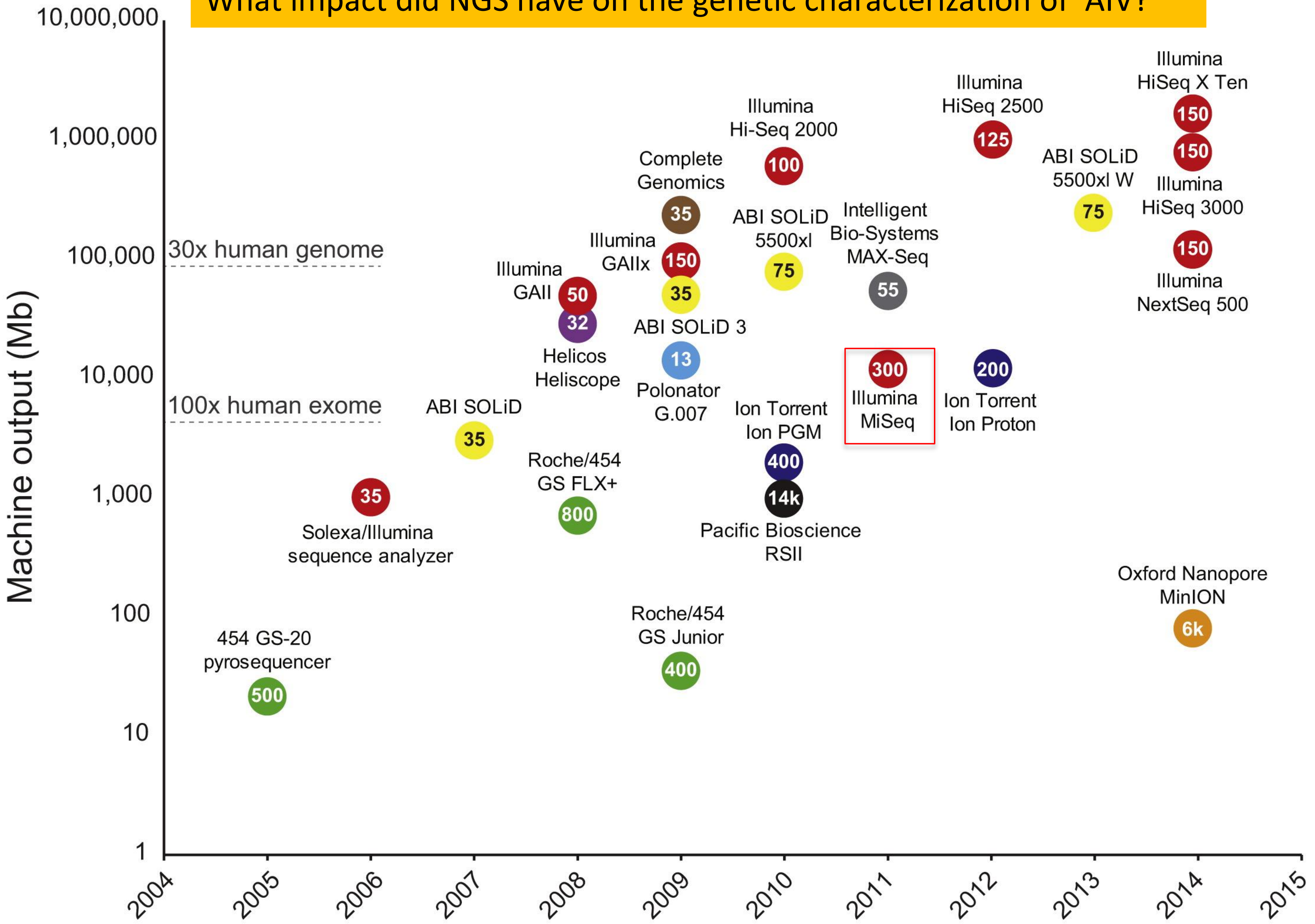
- *in situ* sequencing [**2013**]
- Fluorescent in situ sequencing (FISSEQ) – ReadCoor
- Spatial transcriptomics

High-Throughput Sequencing (HTS)



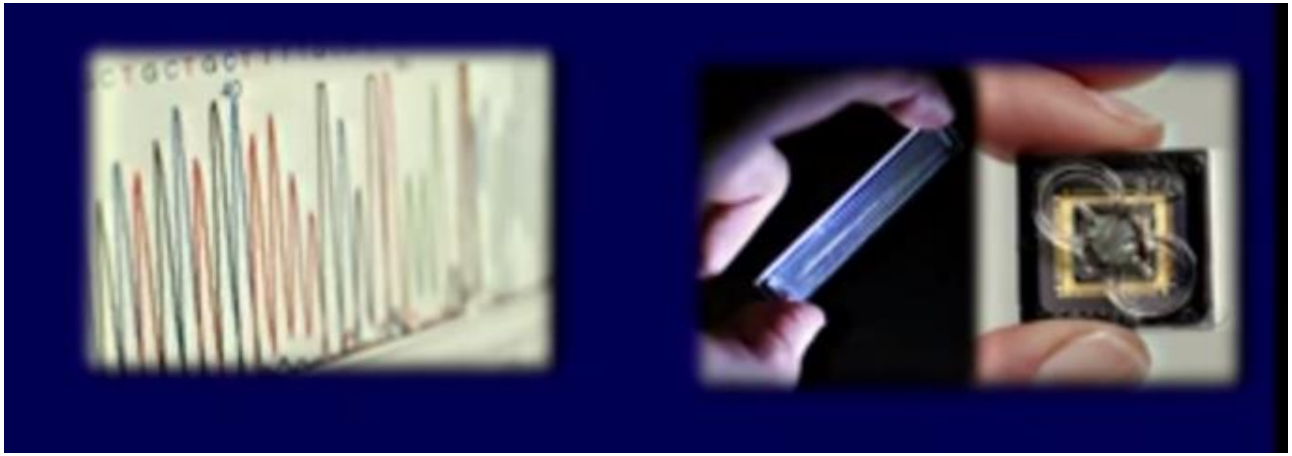
Jason et al., 2015, Molecular Cell, 58(4), 586-597

What impact did NGS have on the genetic characterization of AIV?



Jason et al., 2015, Molecular Cell, 58(4), 586-597

Sequencing an Influenza A virus full genome (13.5Kb) at a FAO/OIE reference center/lab (IZSVe)



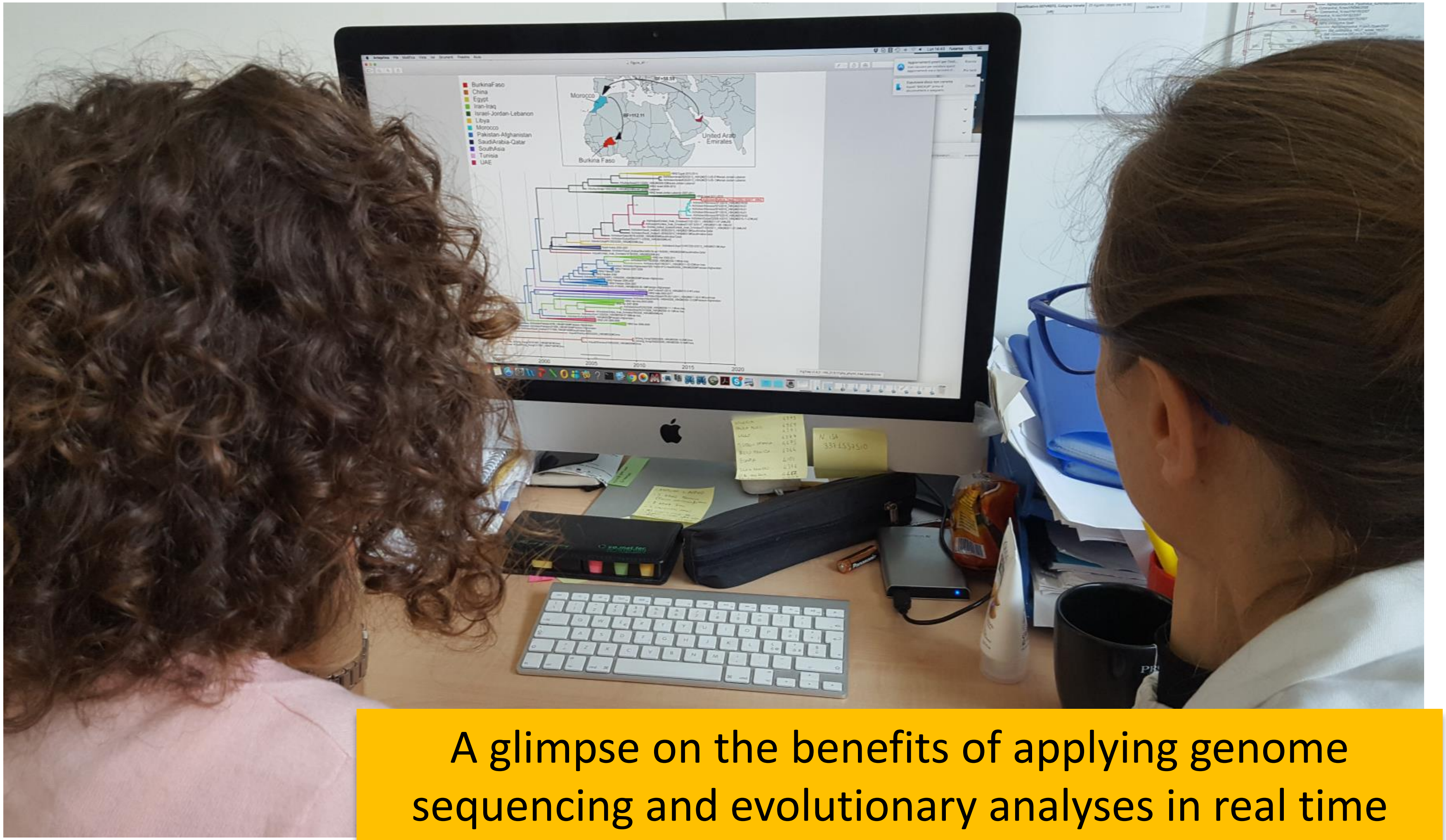
1st Generation Sequencing
(*Sanger*)

Time: @ 2 weeks
Cost: @340 $

2nd Generation Sequencing
(*Illumina MiSeq*)

Time: 3 days
Cost: @70 $

Istituto Zooprofilattico Sperimentale delle Venezie



A glimpse on the benefits of applying genome sequencing and evolutionary analyses in real time during an outbreak: a practical example

Istituto Zooprofilattico
Sperimentale delle Venezie

Identification of the H9N2 subtype in West Africa

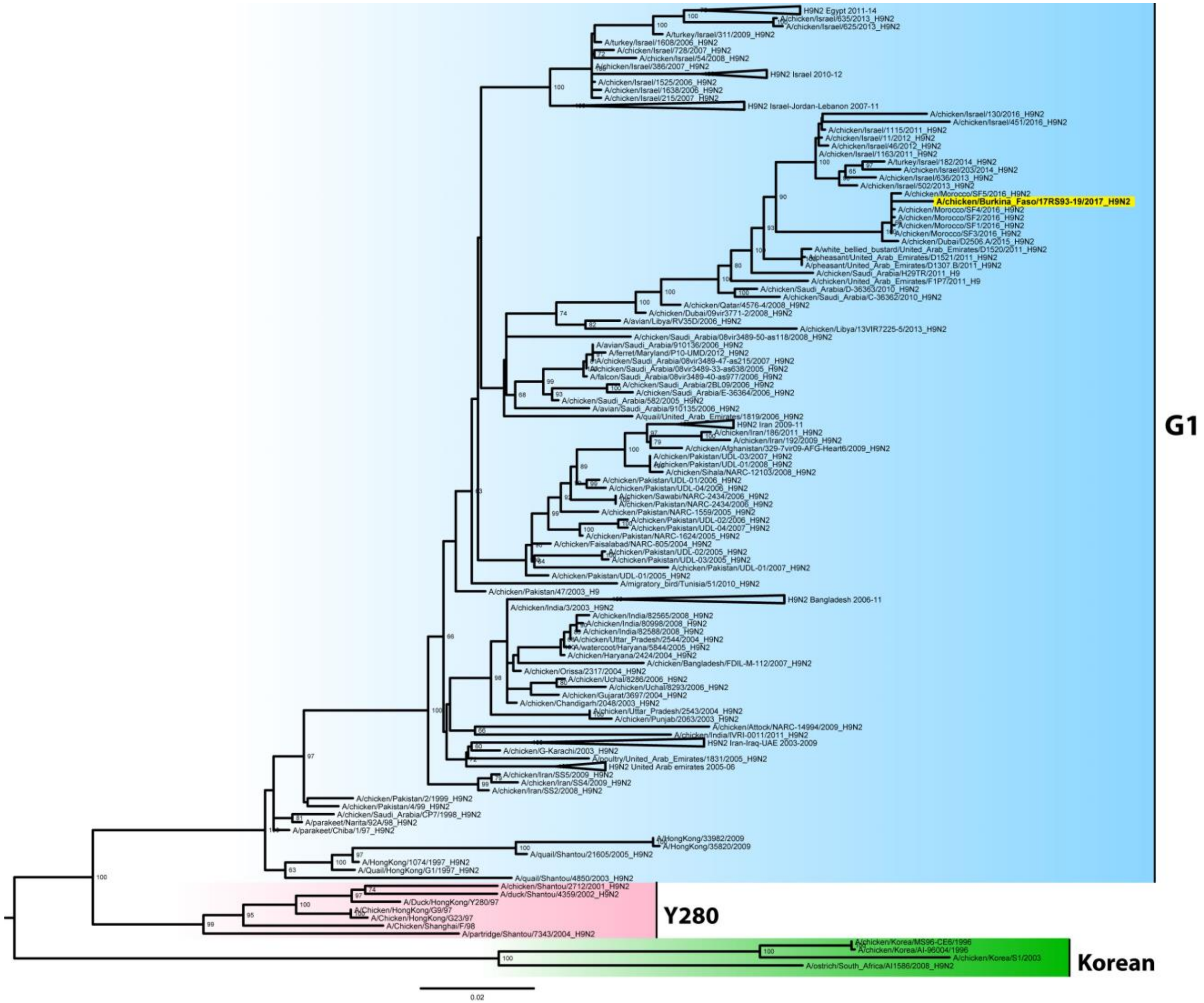
February 2017: a layer farm experiencing decreased egg production and respiratory signs was found positive for the H9N2 AIV

Minoungou, Zecchin et al 2017. EID accepted

Practical uses of genome sequences

Data provided rapidly (in real-time) in case of an outbreak

- Which type of H9 lineage had infected the farm? The G1, Y280 or Y439 (Korean) lineage?



G1 lineage:

- detected in humans
- well adapted to galliformes

Minoungou, Zecchin et al 2017. EID accepted

Practical uses of genome sequences

Data provided rapidly (in real-time) in case of an outbreak

- Where did the virus come from?


11/1995
N
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth


2/1998
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth


8/2001
N
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth


3/2004
US Dept of State Geographer
© 2017 Google
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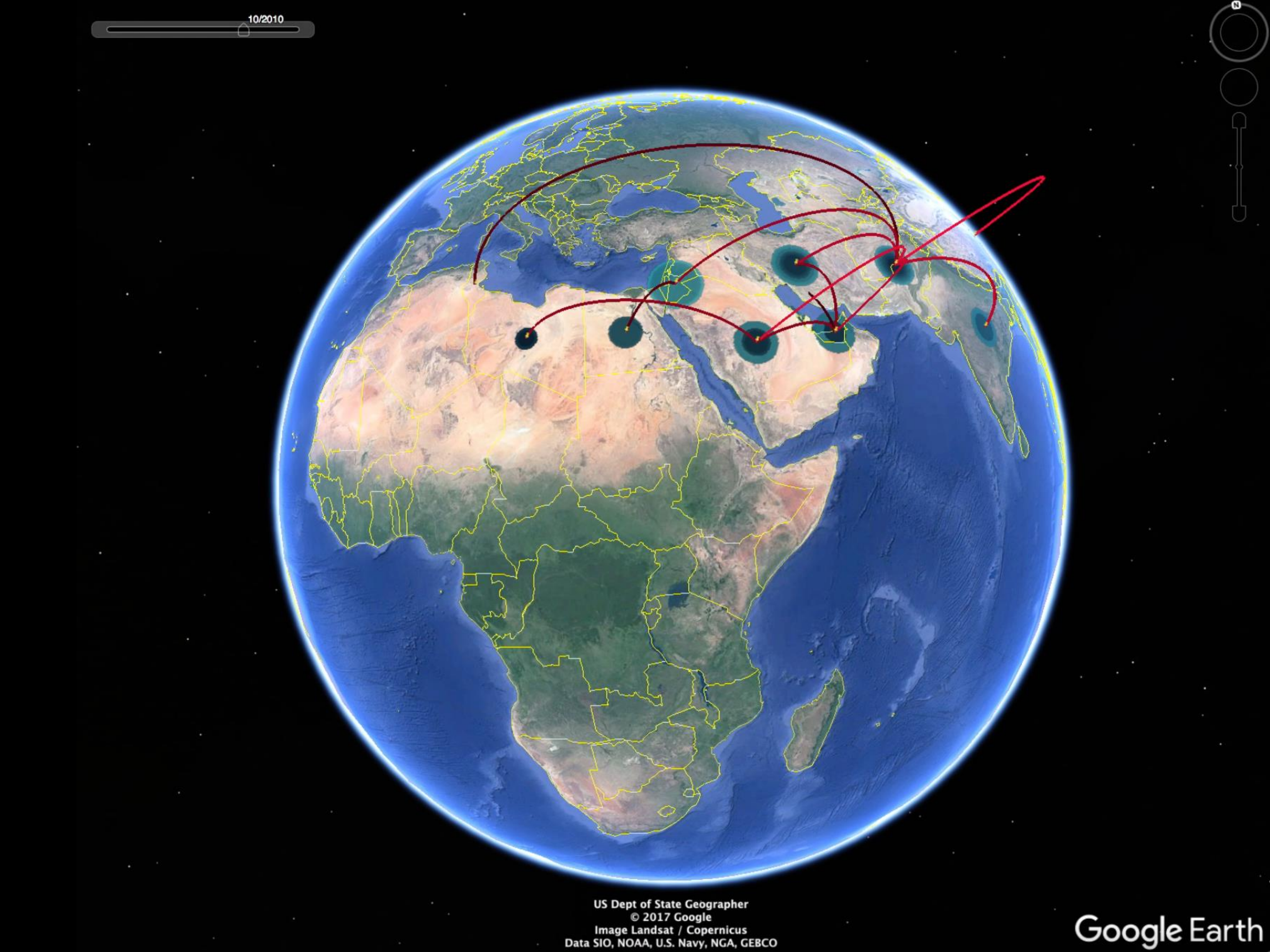
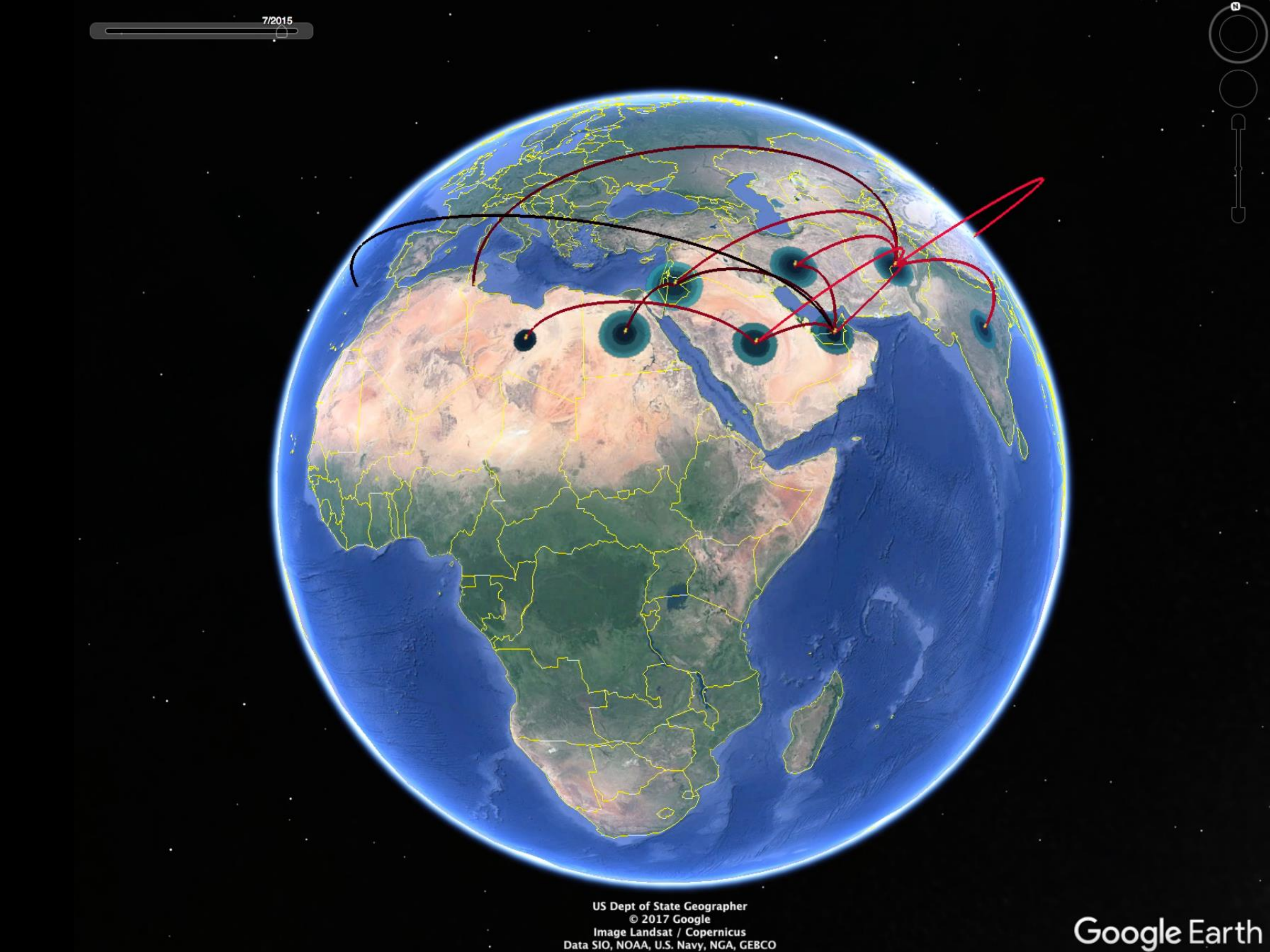
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth


7/2005
N
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth


10/2010
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth



US Dept of State Geographer
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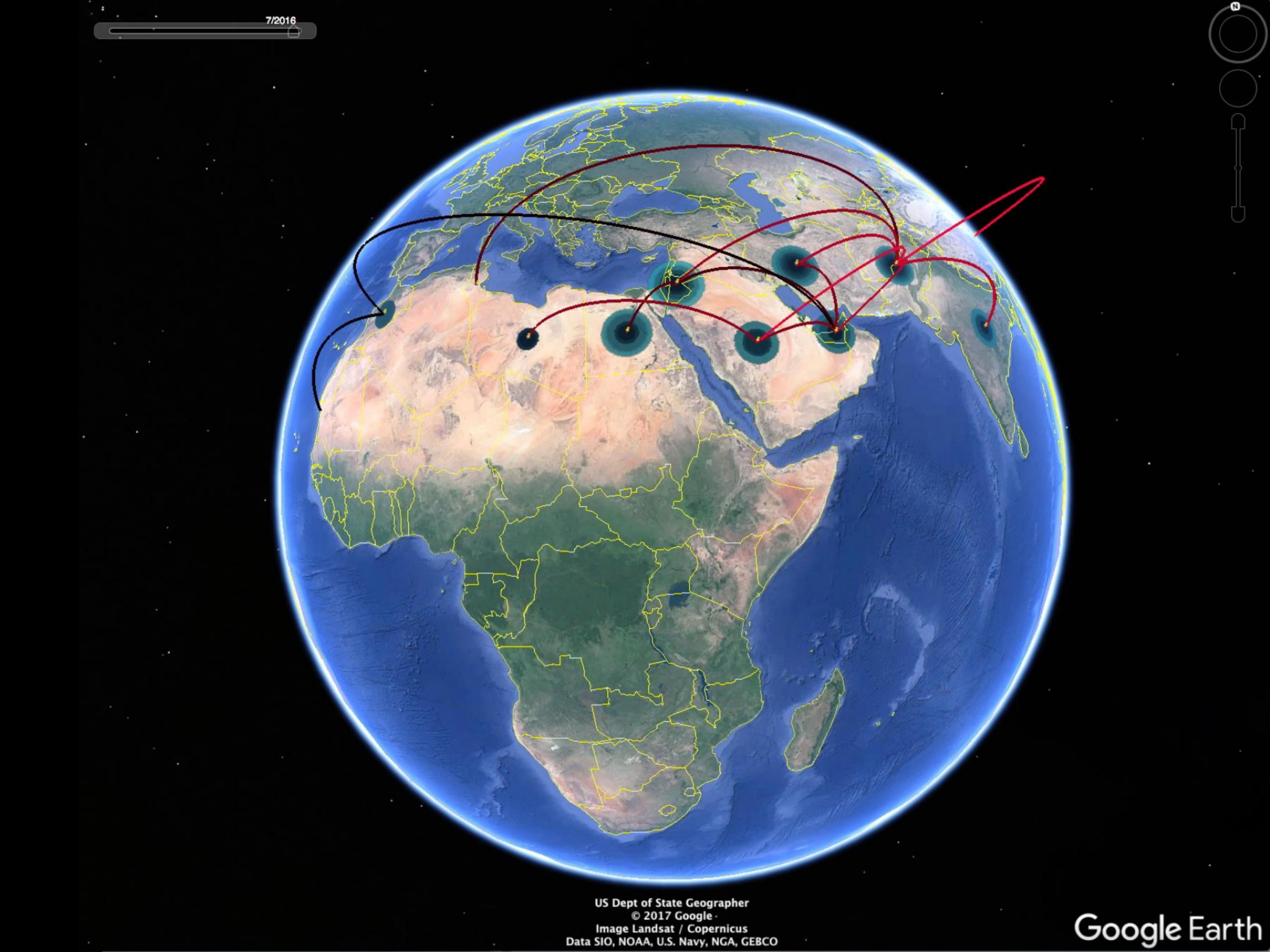
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO



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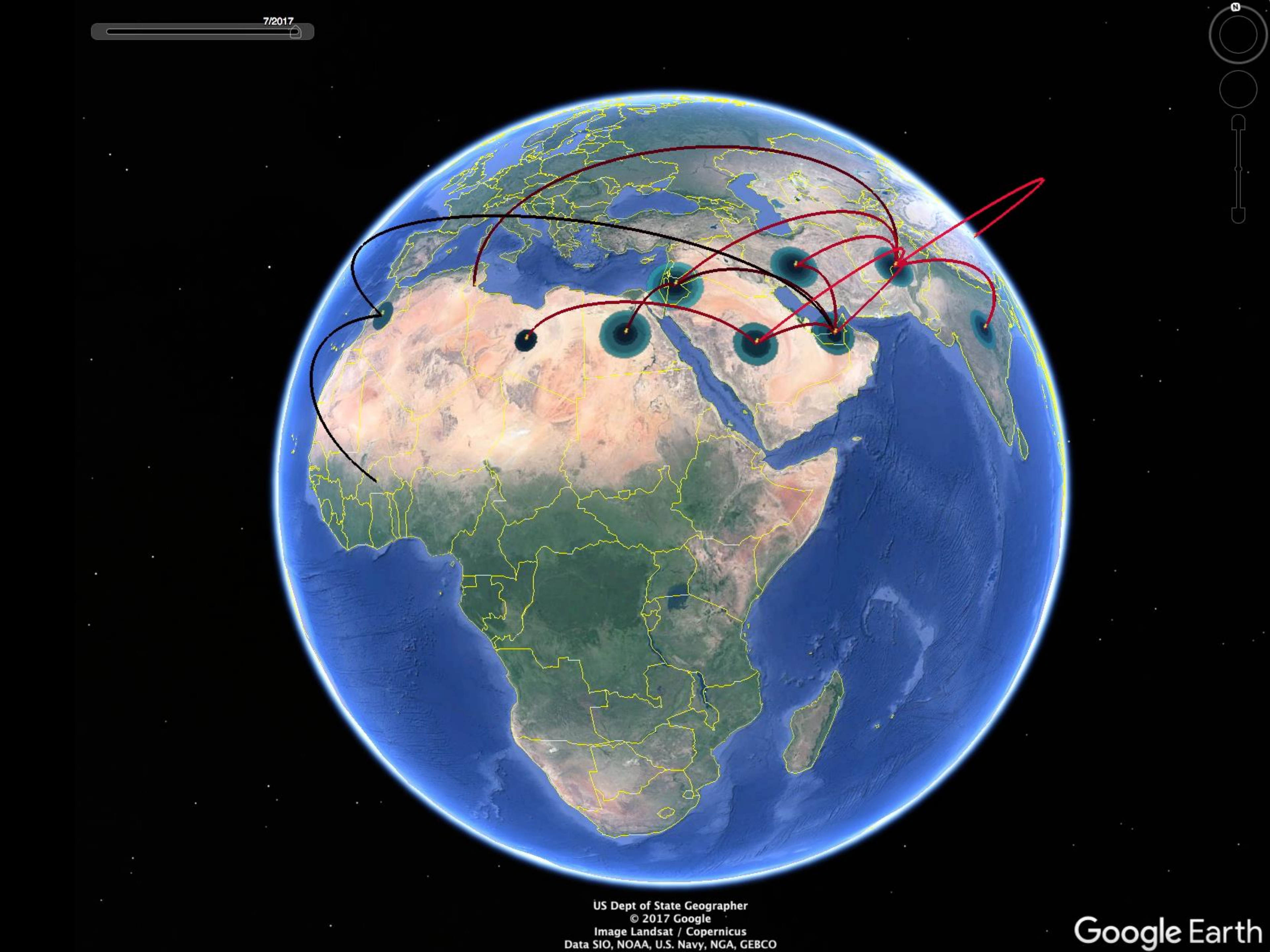
Data SIO, NOAA, U.S. Navy, NGA, GEBCO


7/2017
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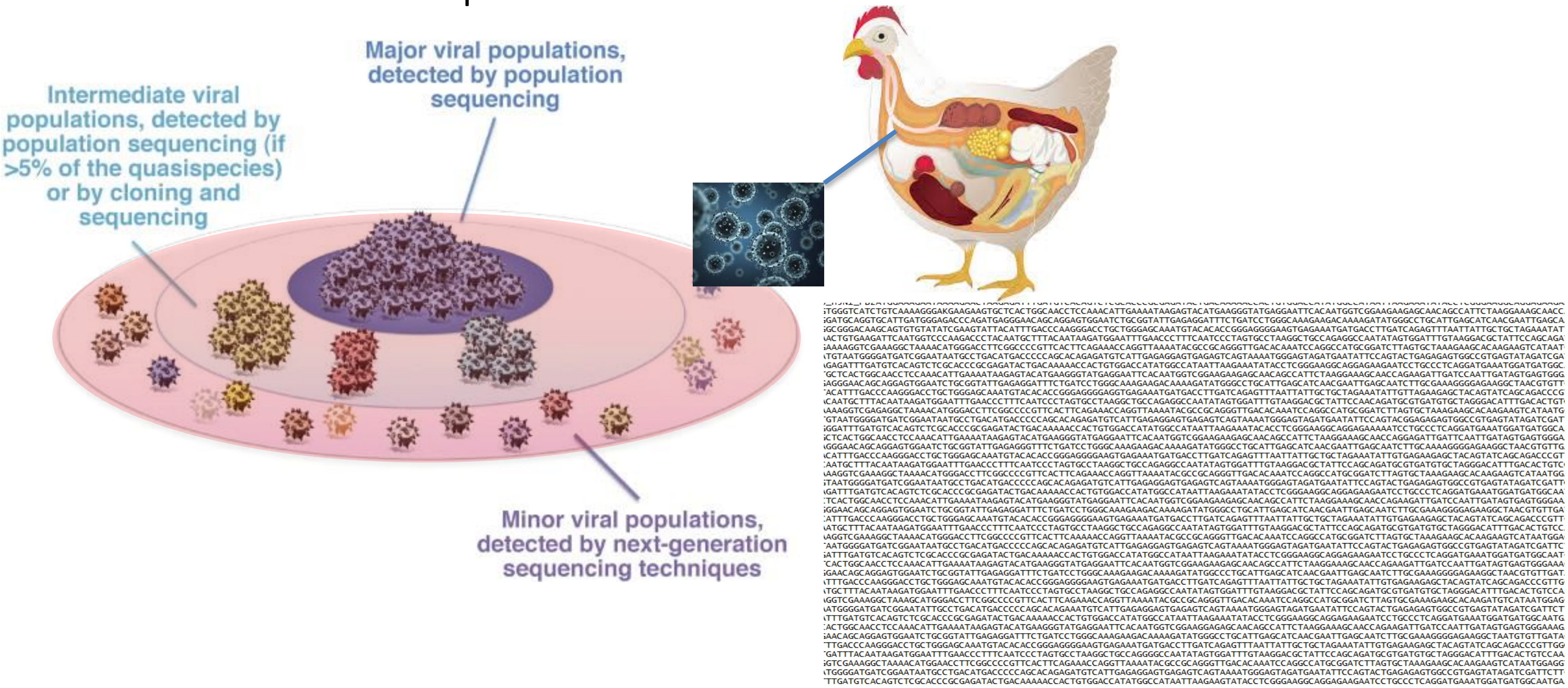
US Dept of State Geographer
© 2017 Google
Image Landsat / Copernicus
Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google Earth

Practical uses of genome sequences

Data provided rapidly (in real-time) in case of an outbreak

- Identification of zoonotic potential



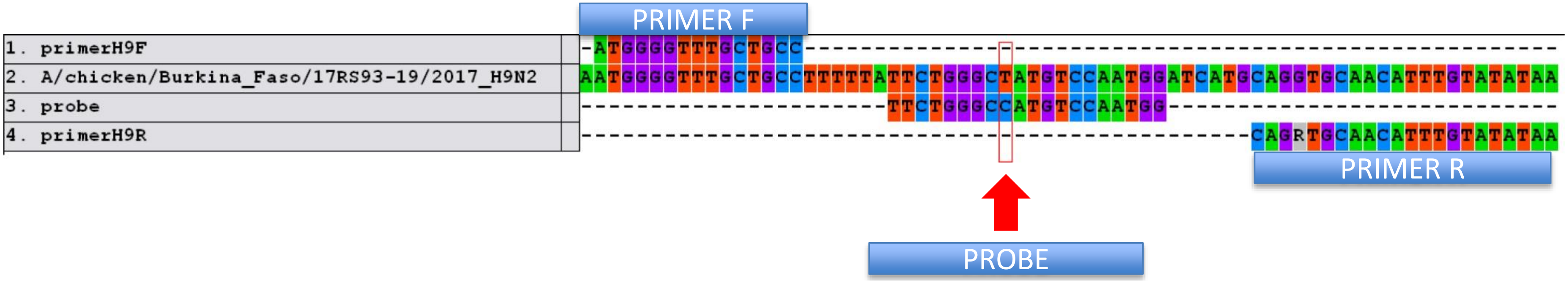
50% of the viral population possessed the amino acid Leucine at position 226 (H3 numbering) of the HA receptor binding site, which entails preferential binding to human-like α2-6-linked sialic acid (SA α2-6) receptors.

Minoungou, Zecchin et al 2017. EID accepted

Practical uses of genome sequences

Data provided rapidly (in real-time) in case of an outbreak

- Identification of mutations with diagnostic implications



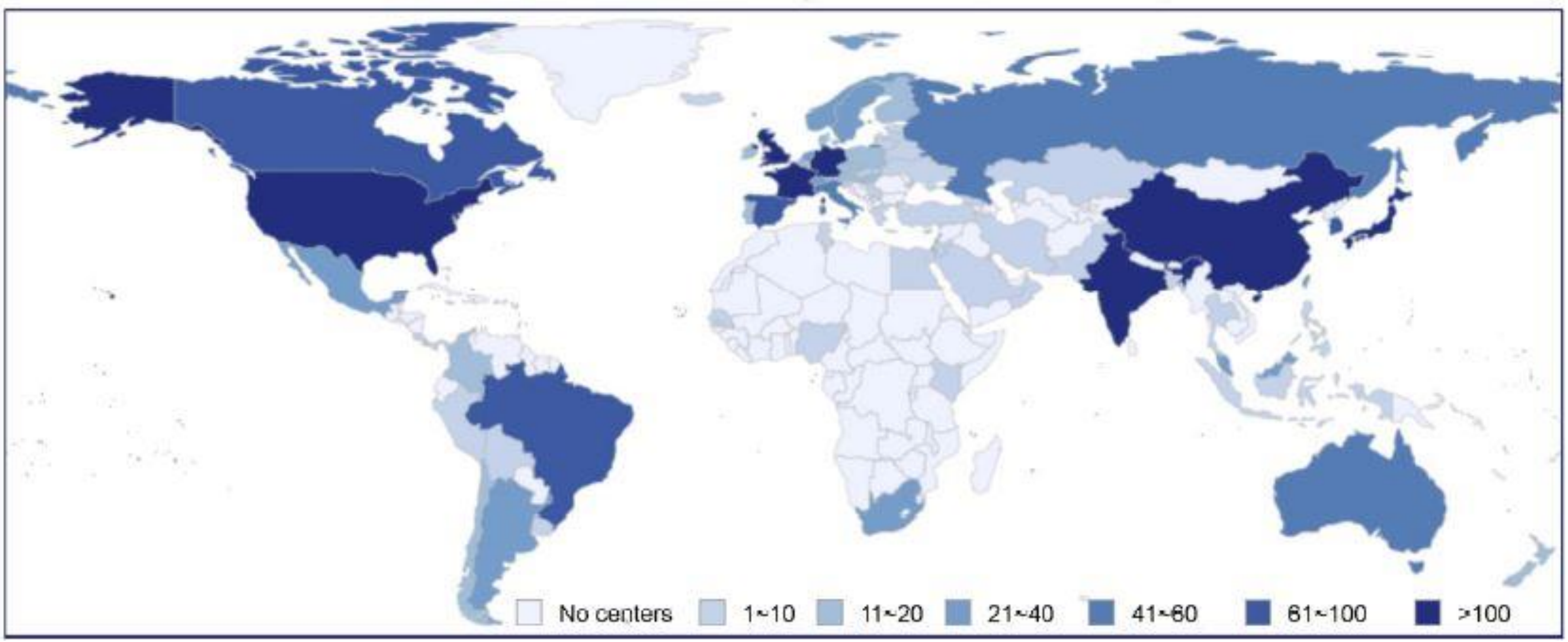
```
1. primerH9F                           -ATGGGGTTTGCTGCC------------------------------------------------------
2. A/chicken/Burkina_Faso/17RS93-19/2017_H9N2   AATGGGGTTTGCTGCCTTTTTATTCTGGGCTATGTCCAATGGATCATGCAGGTGCAACATTTGTATATAA
3. probe                               ----------------------TTCTGGGCCATGTCCAATGG----------------------------
4. primerH9R                           ------------------------------------------------CAGRTGCAACATTTGTATATAA
```

The established RT-qPCRs need to be costantly evaluated and adapted.
Fine tuning for improved performances during outbreaks is necessary

Monne et al, JCM, 2008

Global Sequencing Capacity

Technology accessibility:
Sequencing centers over the world



As of November 2015

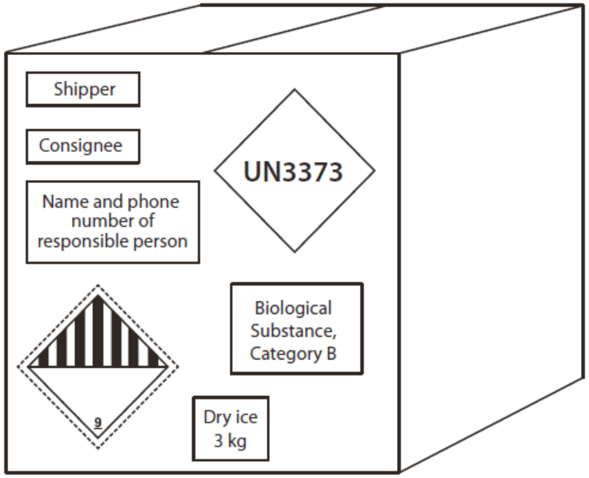
Helmy et al. Applied & Translational Genomics 9 (2016) 15–19

Avian influenza viruses have a global reach: possible actions for the sustainable development of genome sequencing technologies

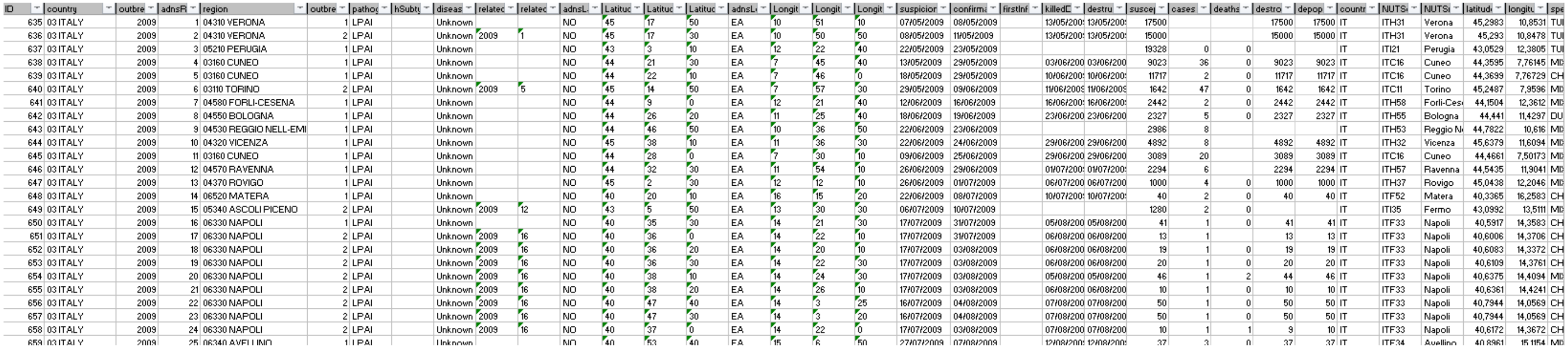
- Using modern sequencing technologies that minimize infrastructure requirements (i.e., MinION by Oxford Nanopore Technologies)
- Increasing research funds for genomic research
- Fostering international collaborations (crucial role for OIE/FAO reference lab/centres and OIE collaborating centers)

Obstacles to sample sharing and generation of evolutionary data

- Sample shipment (cost, logistics)



- Lack of metadata (i.e., date, location, species, farm type, clinical signs, biosecurity and control measures)



ID	country	outbre	adnsR	region	outbre	pathog	hSubty	diseas	relatec	relatec	adnsL	Latituc	Latituc	Latituc	adnsL	Longit	Longit	Longit	suspicior	confirma	firstInf	killedD	destru	suscep	cases	deaths	destro	depop	countr	NUTS	NUTS	latitud	longitu	spe
635	03 ITALY	2009	1	04310 VERONA	1	LPAI		Unknown			NO	45	17	50	EA	10	51	10	07/05/2009	08/05/2009		13/05/200	13/05/200	17500			17500	17500	IT	ITH31	Verona	45,2983	10,8531	TU
636	03 ITALY	2009	2	04310 VERONA	2	LPAI		Unknown	2009	1	NO	45	17	30	EA	10	50	50	08/05/2009	11/05/2009		13/05/200	13/05/200	15000			15000	15000	IT	ITH31	Verona	45,293	10,8478	TU
637	03 ITALY	2009	3	05210 PERUGIA	1	LPAI		Unknown			NO	43	3	10	EA	12	22	40	22/05/2009	23/05/2009				19328	0	0			IT	ITI21	Perugia	43,0529	12,3805	TU
638	03 ITALY	2009	4	03160 CUNEO	1	LPAI		Unknown			NO	44	21	30	EA	7	45	40	13/05/2009	29/05/2009		03/06/200	03/06/200	9023	36	0	9023	9023	IT	ITC16	Cuneo	44,3595	7,76145	MI
639	03 ITALY	2009	5	03160 CUNEO	1	LPAI		Unknown			NO	44	22	10	EA	7	46	0	18/05/2009	29/05/2009		10/06/200	10/06/200	11717	2	0	11717	11717	IT	ITC16	Cuneo	44,3699	7,76729	CH
640	03 ITALY	2009	6	03110 TORINO	2	LPAI		Unknown	2009	5	NO	45	14	50	EA	7	57	30	29/05/2009	09/06/2009		11/06/200	11/06/200	1642	47	0	1642	1642	IT	ITC11	Torino	45,2487	7,9596	MI
641	03 ITALY	2009	7	04580 FORLI-CESENA	1	LPAI		Unknown			NO	44	9	0	EA	12	21	40	12/06/2009	16/06/2009		16/06/200	16/06/200	2442	2	0	2442	2442	IT	ITH58	Forli-Ces	44,1504	12,3612	MI
642	03 ITALY	2009	8	04550 BOLOGNA	1	LPAI		Unknown			NO	44	26	20	EA	11	25	40	18/06/2009	19/06/2009		23/06/200	23/06/200	2327	5	0	2327	2327	IT	ITH55	Bologna	44,441	11,4297	DU
643	03 ITALY	2009	9	04530 REGGIO NELL-EMI	1	LPAI		Unknown			NO	44	46	50	EA	10	36	50	22/06/2009	23/06/2009				2986	8				IT	ITH53	Reggio N	44,7822	10,616	MI
644	03 ITALY	2009	10	04320 VICENZA	1	LPAI		Unknown			NO	45	38	10	EA	11	36	30	22/06/2009	24/06/2009		29/06/200	29/06/200	4892	8		4892	4892	IT	ITH32	Vicenza	45,6379	11,6094	MI
645	03 ITALY	2009	11	03160 CUNEO	1	LPAI		Unknown			NO	44	28	0	EA	7	30	10	09/06/2009	25/06/2009		29/06/200	29/06/200	3089	20		3089	3089	IT	ITC16	Cuneo	44,4661	7,50173	MI
646	03 ITALY	2009	12	04570 RAVENNA	1	LPAI		Unknown			NO	44	32	30	EA	11	54	10	26/06/2009	29/06/2009		01/07/200	01/07/200	2294	6		2294	2294	IT	ITH57	Ravenna	44,5435	11,9041	MI
647	03 ITALY	2009	13	04370 ROVIGO	1	LPAI		Unknown			NO	45	2	30	EA	12	12	10	26/06/2009	01/07/2009		06/07/200	06/07/200	1000	4	0	1000	1000	IT	ITH37	Rovigo	45,0438	12,2046	MI
648	03 ITALY	2009	14	06520 MATERA	1	LPAI		Unknown			NO	40	20	10	EA	16	15	20	22/06/2009	08/07/2009		10/07/200	10/07/200	40	2	0	40	40	IT	ITF52	Matera	40,3365	16,2583	CH
649	03 ITALY	2009	15	05340 ASCOLI PICENO	2	LPAI		Unknown	2009	12	NO	43	5	50	EA	13	30	30	06/07/2009	10/07/2009				1280	2	0			IT	ITI35	Fermo	43,0992	13,5111	MI
650	03 ITALY	2009	16	06330 NAPOLI	1	LPAI		Unknown			NO	40	35	30	EA	14	21	30	17/07/2009	31/07/2009		05/08/200	05/08/200	41	1	0	41	41	IT	ITF33	Napoli	40,5917	14,3583	CH
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652	03 ITALY	2009	18	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	36	20	EA	14	20	10	17/07/2009	03/08/2009		06/08/200	06/08/200	19	1	0	19	19	IT	ITF33	Napoli	40,6083	14,3372	CH
653	03 ITALY	2009	19	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	36	30	EA	14	22	30	17/07/2009	03/08/2009		06/08/200	06/08/200	20	1	0	20	20	IT	ITF33	Napoli	40,6109	14,3761	CH
654	03 ITALY	2009	20	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	38	10	EA	14	24	30	17/07/2009	03/08/2009		05/08/200	05/08/200	46	1	2	44	46	IT	ITF33	Napoli	40,6375	14,4094	MI
655	03 ITALY	2009	21	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	38	20	EA	14	26	10	17/07/2009	03/08/2009		06/08/200	06/08/200	10	1	0	10	10	IT	ITF33	Napoli	40,6361	14,4241	CH
656	03 ITALY	2009	22	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	47	40	EA	14	3	25	16/07/2009	04/08/2009		07/08/200	07/08/200	50	1	0	50	50	IT	ITF33	Napoli	40,7944	14,0569	CH
657	03 ITALY	2009	23	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	47	30	EA	14	3	20	16/07/2009	04/08/2009		07/08/200	07/08/200	50	1	0	50	50	IT	ITF33	Napoli	40,7944	14,0569	CH
658	03 ITALY	2009	24	06330 NAPOLI	2	LPAI		Unknown	2009	16	NO	40	37	0	EA	14	22	0	17/07/2009	03/08/2009		07/08/200	07/08/200	10	1	1	9	10	IT	ITF33	Napoli	40,6172	14,3672	CH
659	03 ITALY	2009	25	06340 AVELLINO	1	LPAI		Unknown			NO	40	53	40	EA	15	6	50	27/07/2009	07/08/2009		12/08/200	12/08/200	37	3	0	37	37	IT	ITF34	Avellino	40,8961	15,1154	MI

Obstacles to data sharing prevent the exploitation of the benefit of evolutionary analyses: considerations from an OIE/FAO RL/RC (IZSVe)

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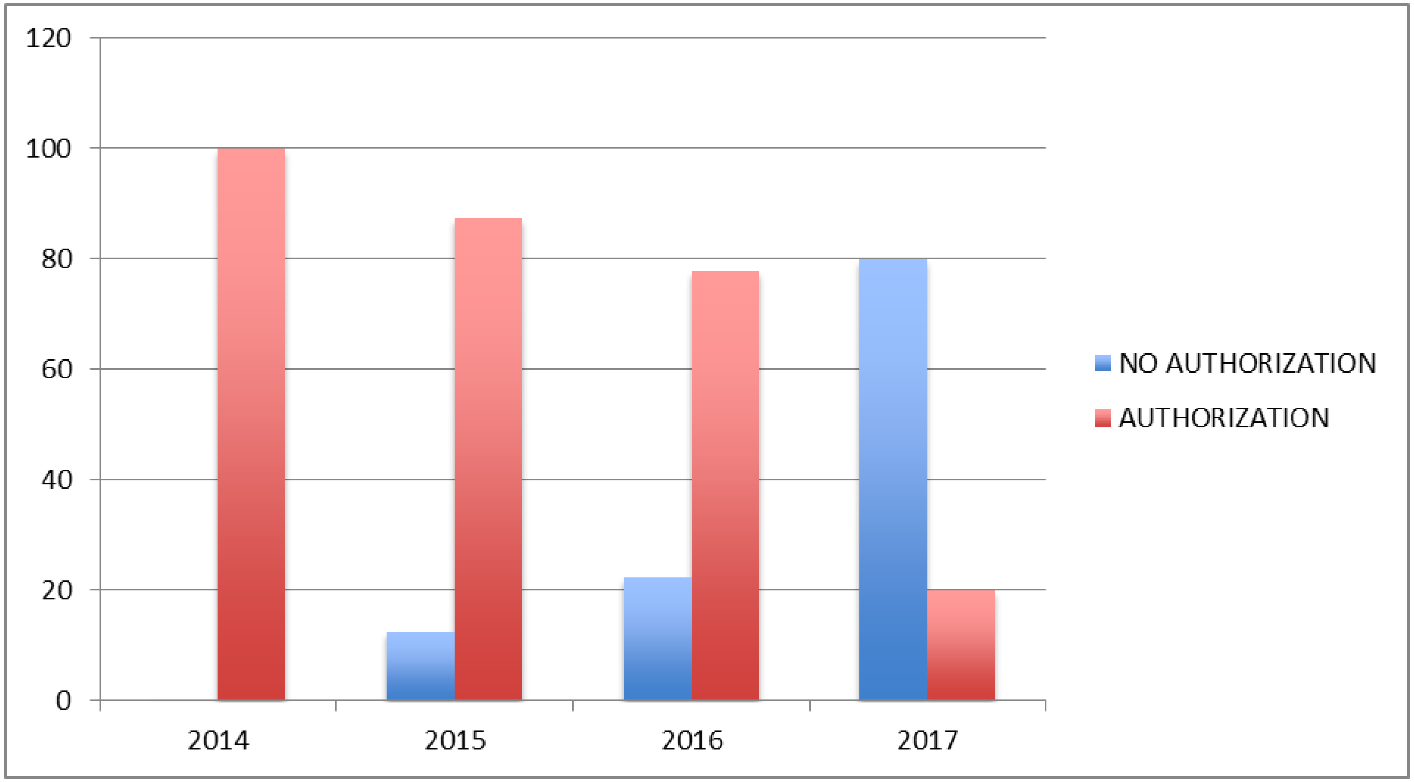
Sperimentale delle Venezie

Immediate release of sequences in public databases in the last four years at a FAO/OIE RC/RL (IZSVe)



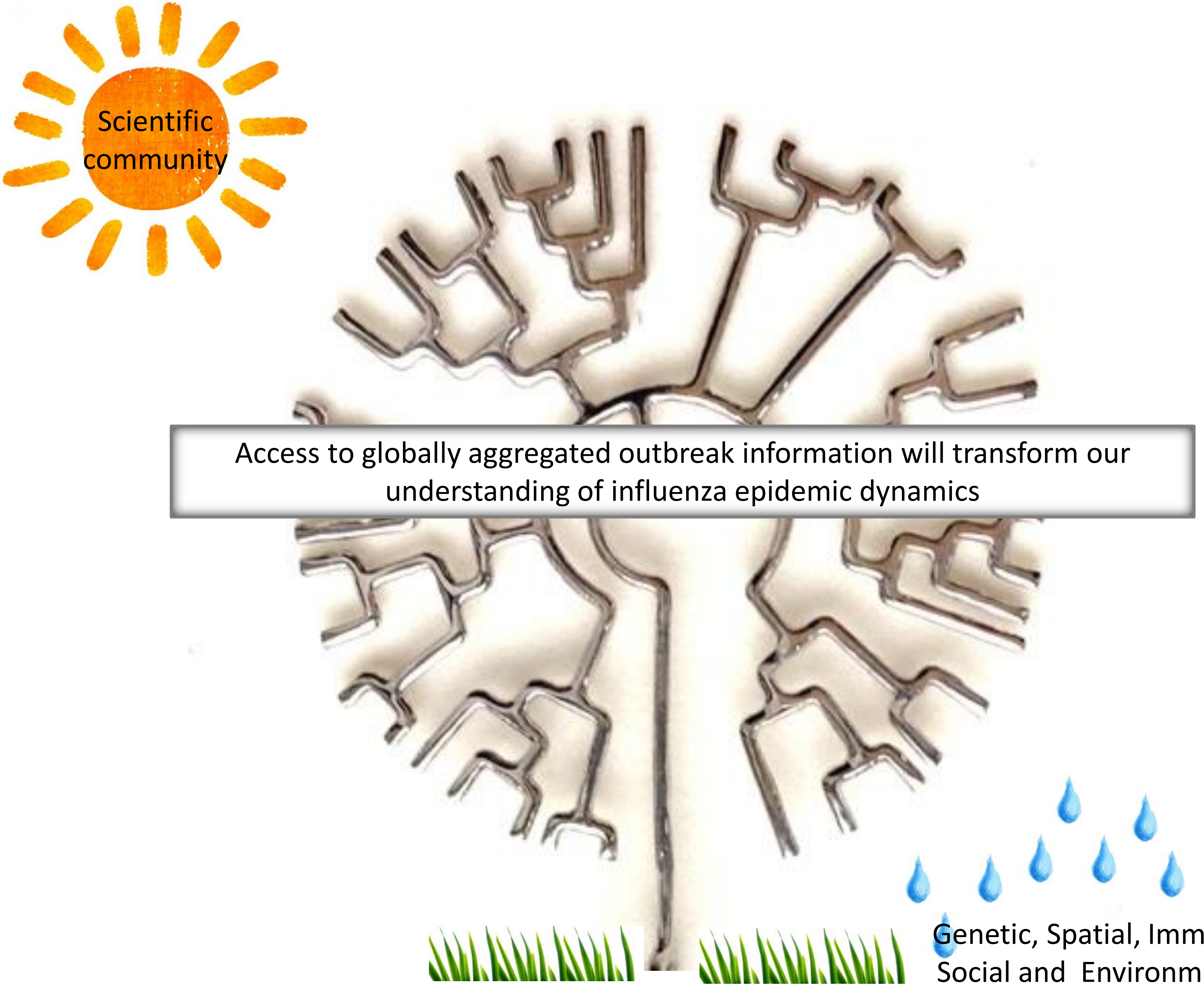
From the evolution of technology to understanding the evolution

- Avian influenza viruses have a truly global reach and cannot be fully understood by studies limited by a spatial or temporal range.
- In an increasingly connected world, rapid sequencing and standardized protocols to collect samples and data from outbreaks should be established.
- Investing in computational and genetic technologies will be essential to generate data which can be used to build tailored control systems and research agendas.

From the evolution of technology to understanding the evolution

- The greatest obstacle to understanding the full public health potential of influenza data is social, not technological.

- Global and multi-level efforts are essential (1) to educate to the benefits of virus and data sharing and (2) to develop universal guidelines to assure access to avian influenza viruses and data in real time



Scientific community

Access to globally aggregated outbreak information will transform our understanding of influenza epidemic dynamics

Genetic, Spatial, Immunological, Social and Environmental DATA

Istituto Zooprofilattico Sperimentale delle Venezie

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RC IZS VE 14/09, Italian Ministry of Health

Istituto Zooprofilattico
Sperimentale delle Venezie

Thank you for your attention!

Istituto Zooprofilattico Sperimentale delle Venezie

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