Intrinsic and extrinsic factors for the emergence of zoonotic viruses at the animalhuman interface

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PARIS DIDEROT





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Emergence at the animal-human interface



Stages of emergence and barriers





3

Stages of emergence and barriers



Stages of emergence and barriers



Barriers





Cell *entry expression/replication exit*

access to target organ diffusion (amplification) escape host responses



between hosts transmission survival escape immunity

Determinants and factors

intrinsic viral determinants

host determinants extrinsic factors

MERS epidemiology



MERS epidemiology



Origin of the virus and source of infection



MERS-CoV evolution in camels





- MERS-CoV related to human viruses detected and isolated from dromedary camels
- Circulation of different lineages
- Evidence for recombination
- Identity among quasispecies
- Experimental infections in dromadary camels (mild disease; high levels of viral shedding)

Nowotny et al. Eurosurveillance 2014

Briese et al. mBio 2014

Sabir et al. Science 2016



Influenza A viruses





H5N8 exposure



Widespread in Europe in wild birds and poultry - **no human cases** detected ¹³

H7N9 exposure ford and Agricultur

- 31 March 2013 1st detections of human cases in China (2 in Shanghai ; 1 in Anhui)
- Source : poultry (markets)
- urban settings initially; recent spread to rural areas
- Low pathogenicity for birds
 Evolution to highly pathogenic form in 2017

Figure 2: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset, 2013-2017





Humans

- Source poultry :
- limited human-to-human transmission documented
- Severity of infections total 798 cases 320 deaths (WHO – 29/09/2016)

Genome origin

H5N1



H7N9



H1N1v

15

H3N2v swine influenza viruses triple reassortant 2005-2010 Human cases 2011-12 Human cases of H3N2v H1N1pdm09 of H3N2v A/Minnesota/11/2010 Classical Swine - North American Lineage /lowa/09/2011 Avian - North American Lineage A/lowa/07/2011 A/lowa/08/2011 – A/Indiana/10/2011 Triple reassortant viruses of swine origin Human Origin H3N2 нΔ Eurasian Swine Lineage A/Indiana/08/2011 A/swine/Indiana/653/2011 /swine/Pennsylvania/9256/2010 H3N2v 422 cases - 24 hospitalized; 1 death ٠ H1N1v : 20 cases H1N2v: 11 cases (29/09/2017 - CDC) Mostly mild disease (ILI) Human viruses ٠ Source : exposure to swine (agricultural fairs) • Some cases of human-to-human transmission • documented – estimated R0 ≈ 0.5 H3N2v viruses antigenically related to 1995 • A/mallard/Mississippi/360/2010 human viruses 0.05

Intrinsic viral determinants determinants of cell and host infection

SARS-CoV Evolution



S gene maximum likelihood PAUP

Kan et al. 2005 JV 79:11892



MERS-CoV Receptor specificity



van Doremalen et al.2014 JVI

MERS-CoV Receptor expression

DPP4 expression



Widagdo et al.2016 JVI

Binding to sialic acid receptors



Distribution of HA receptors In respiratory tract

Shynia et al. Nature 2006 Van Riel et al. Science 2006

Avian virus A/duck/Mongolia/301/01

HA and NA glycosylation

8



Evolution of glycosylation of human H3 beween 1968 and 2007

246

285

A/Brisbane/10/07

Variations according to species

Evolution upon adaptation to new species

Impact on HA – NA balance

HA / NA Balance

NA and interspecies transmission



Effect of PB2 residue 627 on multiplication of avian viruses in the upper respiratory tract of mice

		Virus titer (log PFU)				
Virus	PB2627	lungs	NT	spleen	heart	
						627 🎝 🎆
VN1203/04	Lvs	7.2	4.6	4.9	2.1	
VN1204/04	Glu	5.7	2.3	<	3.4	
VN1203PB2-627E	Glu	3.3	<	2.1	<	
VN1204PB2-627K	Lys	8.2	6.6	7.3	6.8	PB2627 Lys
		()				a star
	Glu	0.0	< 5 5	nt t	nt	200 🏊
Mai/NYPB2-02/K	Lvs	0.0	5.5	nt	nt	
	Glu	3.1	< 	nt .	nt	
VD5PB2-627K	Lys	5.8	5.3	nt	nt	
Balb/c mice infected	i.n.; virus titro	ation in org	gans at day 3 Glu			33°C
PB2 ₆₂₇ Glu			ys		R.	2 37° ¢

Pathogenicity determinants in the polymerase

A36T > polymerase activity and vince to infunce cells. Mouse adapted pdm Zhu et al., 2012 T851 > polymerase activity and vince recise cells. Mouse adapted pdm Bussey et al., 2011 T971 > polymerase activity and vince. Bussey et al., 2011 T971 > polymerase activity and vince. Bussey et al., 2011 T971 > polymerase activity and replication in human and ported pdm Bussey et al., 2011 T971 > polymerase activity and replication Anose adapted pdm Bussey et al., 2011 T971 > polymerase activity, viral growth in mice Bussey et al., 2011 T971 > polymerase activity, viral growth and pathogenesis. H7N9 in mice Bussey et al., 2011 T972 > polymerase activity, viral growth and pathogenesis. H7N9 in mice Hiromoto et al., 2004 T972 > polymerase activity and viral growth. H5N1 in ferrets Linster et al., 2014 L1733 > polymerase activity and viral growth. H5N1 & pdm in mice Xu et al., 2012 T972 P9N Mitochondrial localization. <ipn expression.=""> pathogenicity. H1N1 & H5N1 in mice Ku et al., 2012 T974 > viral replication and virulence. > binding and inhibition to MAVS. Polymerase activity, and replication and pathogenicity. H1N1 & H5N1 in mice Vang at al., 2010 <</ipn>	PA	F35I	> polymerase activity and virulence in mice. Serially passaged pdm in mice	Sever et al. 2012
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Rodriguez-Frandsen et al. 2015 Virus Res



Comparative interactomics of PB2 with the UPS

correlation w/ origin and duration of circulation of PB2 in humans

SARS-CoV and MERS-CoV evasion of innate responses



de Wit et al.2016 Nature Rev Microbiol

Intrinsic viral determinants determinants of transmission

Airborne transmission in ferrets





Herfst et al Science 2012



Airborne transmissible



Substitutions confering airborne transmissibility to H5N1 (reassortant) viruses

HA N224K, Q226L (receptor specificity) HA N158D (glycosylation sequon) HA T318I (trimer interface) HA Q222L, G224S (receptor specificity) HA T156A (glycosylation sequon) HA H103Y (trimer interface) PB2 E627K

Imai et al Nature 2012

Herfst et al Nature 2012



Markers of Airborne transmissibility in H5N1 in nature

Minimum mutations required in HA according to: Herfst et al (left column) Imai et al. (right column)

Blue = 5 nt changes Green= 4 nt changes Orange = 3 nt changes

Russel et al Science 2012

H7N9 transmissibility in ferrets



Belser et al 2016 JVI

H7N9 fusion pH threshold



→ Lower fusion pH threshold for 3rd wave H7N9 viruses

Belser et al 2016 JVI

HP-H7N9 transmissibility





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Imai et al 2017 Cell Host & Microbes

Transmission other intrinsic factors to consider

Survival in the environment H5N1: in dejections (7d at 20°C, 35d at 4°C);water (105d) MERS-CoV: stability >> 72h in camel milk

Ability to infect/disseminate w/in host (replication site, virus yield, ..) Efficiency of replication Fitness and competitiveness Escape host response Virus population diversity





van Doremalen et al, 2015 Eurosurveillance

Transmission other intrinsic factors to consider

Survival in the environment

H5N1: in dejections (7d at 20°C, 35d at 4°C);water (105d) MERS

- Ability to infect/disseminate w/in host
- (replication site, virus yield, ..)
- Efficiency of replication
- Fitness and competitiveness
- Escape host response

Virus population diversity (quasispecies)



sH1N1 H3N2 pH1N1

higher mutation frequency for pH1N1

Gene		Mutation		Human isolates	Environmental isolates
НА		G186V	v	81	2
	Receptor binding site	Q226L/I	L	80	2
			1	1	0
NA		A246T	А	80	2
	Deleted to down analytics		Т	1	0
	Related to drug resistance	R292K	R	79	2
			К	2	0
		E627K	E	20	2
	Increased virulence in mice		к	59	0
			V	2	0
PB2	Enhanced transmission in	530.01	D	71	2
	guinea pigs	D701N	N	10	0
	species-associated signature		к	65	1
	positions	K702R	R	16	1
	Increased transmission in		I	5	0
PB1	Ferret	1368V	V	76	2
		87–90 amino acids in length	11AA	3	1
			34AA	10	0
			76AA	3	0
	Increased pathogenicity in mice		87AA	1	0
PB1-F2			90AA	62	1
			101AA	2	0
	altered virulence and antivirus		Ν	75	2
	response in mice	N665	S	6	0
PA	species-associated signature	V100A	V	68	2
	positions		A	13	0
	increase the polymerase				
	activity in mice	L336M	L	81	2
	species-associated signature	K356R	R	81	2
	positions	S409N	N	81	2
NS1	altered virulence in mice	D92E	D	81	2
	altered antiviral response in	N205S	S	81	2
	host	G210R	G	81	2

H7N9 Pathogenicity determinants

Conclusions

- Evaluation of zoonotic potential
 - based on known determinants
 - (CDC inventory http://www.cdc.gov/flu/pdf/avianflu/h5n1-inventory.pdf)
 - importance of genetic context
 - importance of gene constellations
- ightarrow consider knowledge about genetic lineage
- Challenges and uncertainties
 - level of preexisting immunity
 - level of of asymptomatic infections
 - potential for reassortment
 - genetic susceptibility of the population initially exposed
- Multiple complementary sources of information required

Extrinsic Factors Host and Environment

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Host determinants

- Pre-existing immunity
- Genetic susceptibility (e.g. IFITM3)
- **Age** (e.g. ≠ H5N1, H7N9)
- Sex
- Co-morbidities

Male mice are more susceptible to SARS-CoV



Population densities



Curr Top Microbiol Immunol

Geographical extension



Social and Occupational Factors

- Number and type of contacts
- Hospital settings
- Family settings
- Slaughterhouses
- Breeders, animal care takers
- Food-borne transmission respiratory viruses.

Potential for control of Emergence?



Pandemic risk assessment

- Exposure
- Potential for infection in humans level of severity
- Potential for human-to-human transmission
- Potential for spread in the human population

Tools: IRAT (CDC); TIPRA(WHO)

Determinants of Pandemic risk

- Viral factors
- Host factors
- Social factors



MULTIDICIPLINARITY





Thank you for your attention



