Imperial College London

New Vaccines Against Epidemic Infectious Diseases

E. David G. McIntosh AM

MBBS MPH LLM PhD FAFPHM FRACP FRCP&CH FFPM DRCOG DCH Dip Pharm Med

Honorary Clinical Senior Lecturer, Imperial College, London UK

Declaration of Interest

- Dr McIntosh is an employee of Takeda Pharmaceuticals International AG, which is developing vaccines against dengue, norovirus, Zika virus, poliomyelitis virus and influenza
- The views expressed herein are the views of Dr McIntosh and do not necessarily reflect the views of Imperial College or Takeda

Agenda

- Preparedness
- Viruses
  - Ebola
  - Zika
  - Yellow Fever
  - Pandemic influenza
- Resistant organisms
  - *Acinetobacter baumannii*
  - *Pseudomonas aeruginosa*
  - *Enterobacteriaceae*
- Conclusions

Laboratory preparedness and response
With a focus on arboviruses in Europe
Reusken *et al*. Clinical Microbiology and Infection 20 Dec 2017

- The overall global and European health burden of arboviruses results in increasing pressure on laboratory preparedness and response infrastructures
- As timely and accurate diagnosis of cases is one of the main pillars for public health and clinical responses to an infectious disease emergence, inter-epidemic activities could ensure such adequate response
- (Re)emerging infectious disease outbreak preparedness plans should consider the laboratory pillar and be developed in collaboration between reference laboratories and hospital laboratories, and include planning of the strengthening of such local capacity and capability when needed, for example:
  - In case of an outbreak overloading the national reference system
- The current mushrooming of European preparedness networks requires governance:
  - The establishment of collaboration and alignment across the disciplines covered by each of these networks, in order to bring the European preparedness and response to the next level

https://www-sciencedirect-com.iclibezp1.cc.ic.ac.uk/science/article/pii/S1198743X17306833?via%3Dihub

Ebola

Biomedical Advanced Research and Development Authority (BARDA)

- The mission of BARDA is to support the development and procurement of medical countermeasures (MCM) to be made available for chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza, and emerging infectious diseases

- The Division of CBRN Countermeasures within BARDA supports advanced research and development of vaccines, therapeutics, and diagnostics against viral hemorrhagic fever (VHF) caused by viruses of the family *Filoviridae*

Wolfe *et al*. Progress towards a vaccine against Ebola. Vaccine 2 December 2017

Future FDA-licensed vaccine against Ebola

- Since 2006, BARDA has supported the development of over 160 vaccine, drugs, diagnostics or other countermeasures and 34 of these medical countermeasures have achieved FDA approval, clearance, or license to be used to respond to public health emergencies
- Significant progress was made as several promising Zaire Ebola vaccine candidates moved from early development into late stage clinical development
- The near-term goal is to complete development efforts to ensure that at least one FDA-licensed product is available to provide a response capability for future Ebola virus outbreaks
- The long-term goal includes the expansion of the VHF vaccine program to protect against a broader range of filoviruses such as Sudan Ebola virus and Marburg virus

Wolfe *et al*. Progress towards a vaccine against Ebola. Vaccine 2 December 2017

Ebola virus vaccine development

Vaccine	Examples	Comment
Inactivated virus and subunit vaccines		Classic subunit vaccines need improvement in immunogenicity; virus-like particle approach more promising
Non-replicating vaccine vectors	Alphavirus and flavivirus replicons	Use of Venezuelan equine encephalitis and Kunjin virus platforms
	DNA vaccines	First successful vaccination of mice in 1998. Improvements by use of plasmids allowing administration of larger quantities of DNA. More recently: a prime/boost approach
	Recombinant adenovirus-based vectors	First described in 2000. Problem of pre-existing immunity. Development progressing
	Recombinant ZEBOVΔVP30	Through reverse genetics systems. 100% protection in guinea pigs
Replication-competent vaccine vectors	Recombinant vaccinia, CMV, paramyxovirus, rabies. vesicular stomatitis	Vesicular stomatitis rVSV-ZEBOV vaccine efficacious

Marzi and Feldman. Expert Review Vaccines 2014; 13(4): 521-531

Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease

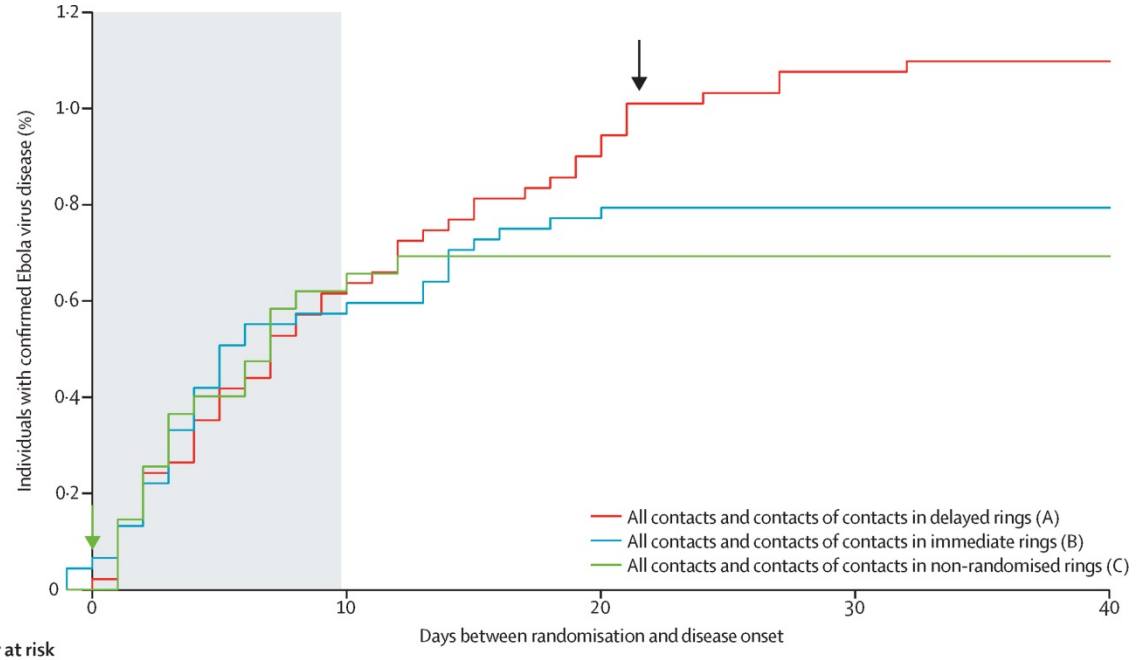
- 4539 contacts and contacts of contacts in 51 clusters randomly assigned to immediate vaccination and 4557 contacts and contacts of contacts in 47 clusters randomly assigned to delayed vaccination

- No cases of Ebola virus disease occurred 10 days or more after randomisation among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters

- Vaccine efficacy was 100% (95% CI 68·9–100·0, p=0·0045)

Henao-Restrepo *et al*. Lancet ID 2017; 389: 505-518

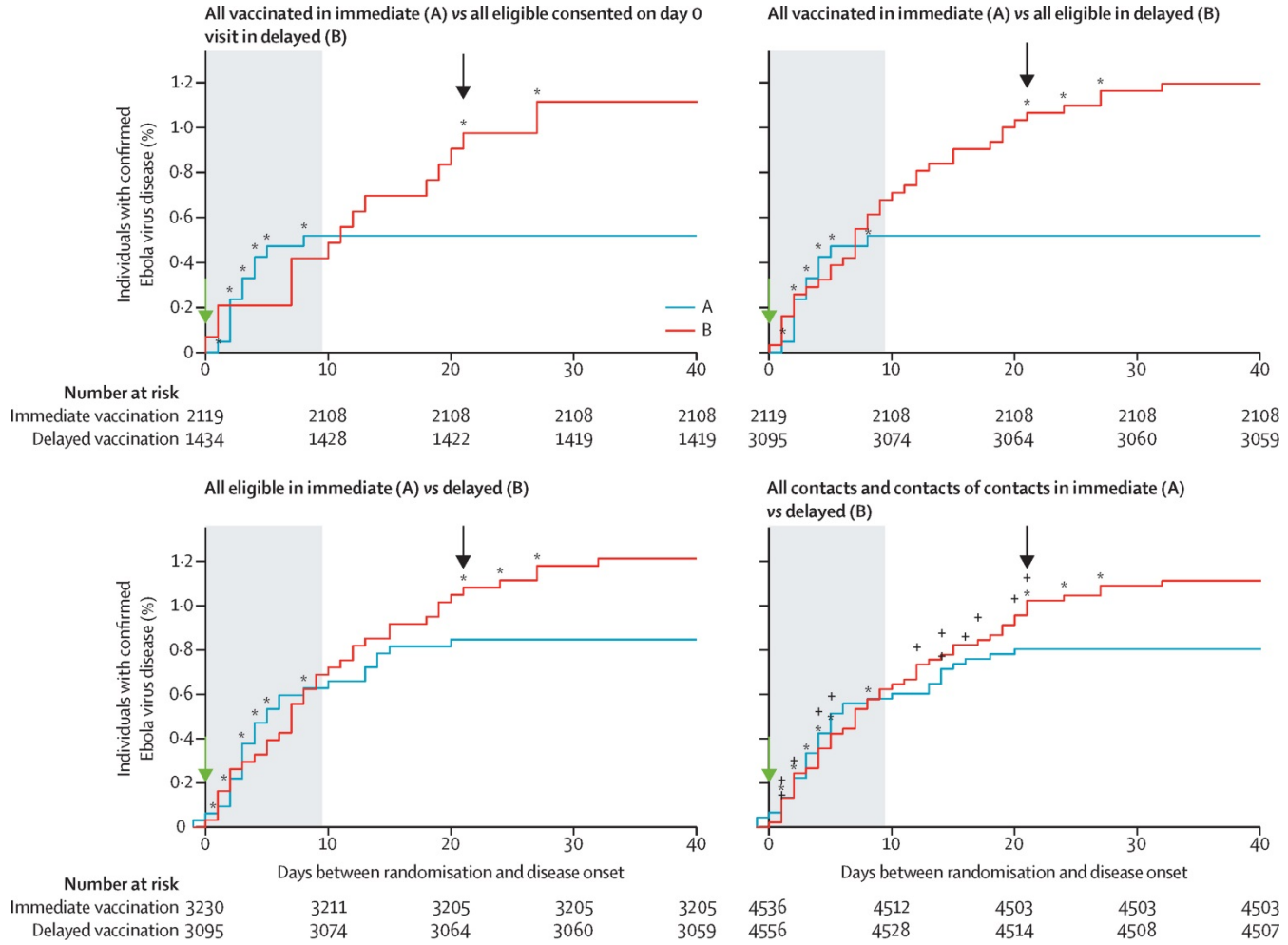
Kaplan-Meier plots for all confirmed cases of Ebola virus disease among all contacts and contacts of contacts in immediate, delayed, and non-randomised clusters



Number at risk					
All contacts and contacts of contacts in delayed rings	4556	4528	4514	4508	4507
All contacts and contacts of contacts in immediate rings	4536	4512	4503	4503	4503
All contacts and contacts of contacts in non-randomised rings	2745	2727	2726	2726	2726

The Lancet 2017 389, 505-518DOI: (10.1016/S0140-6736(16)32621-6)

Kaplan-Meier plots for confirmed cases of Ebola virus disease in different study populations

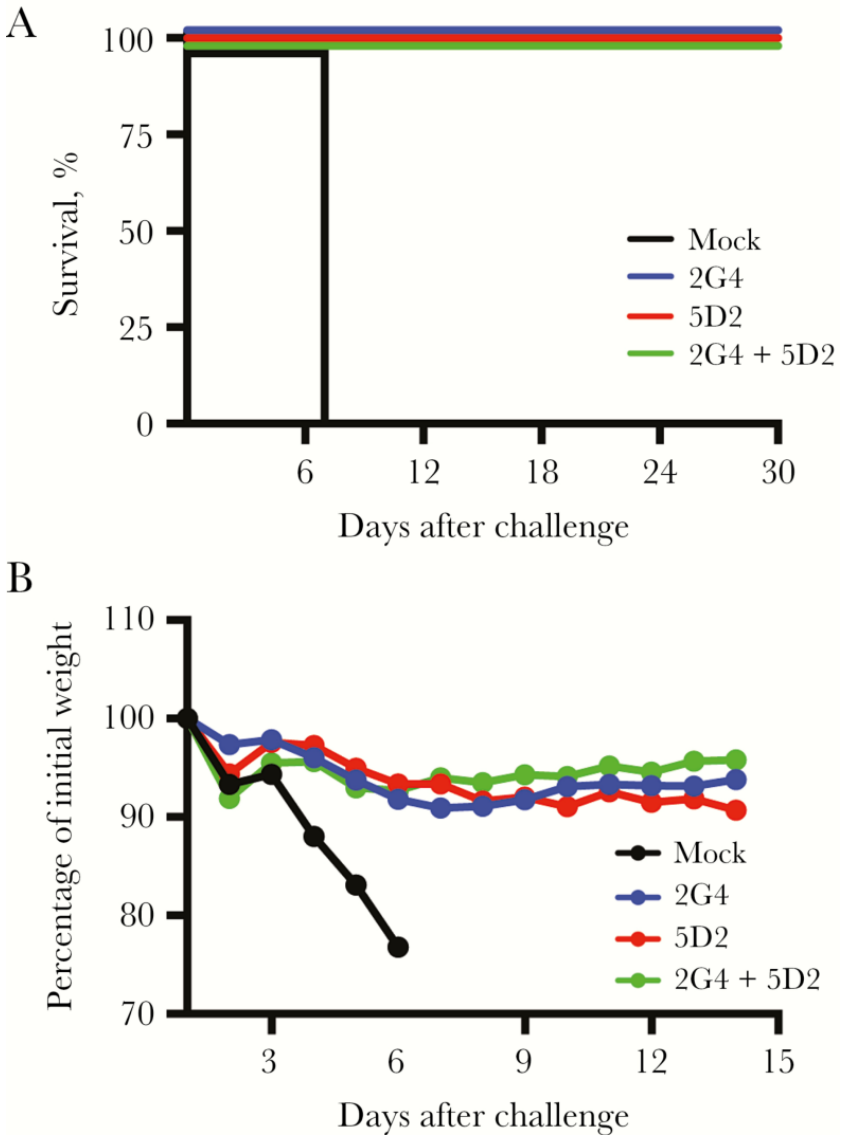


The Lancet 2017 389, 505-518DOI: (10.1016/S0140-6736(16)32621-6)

Sustained adeno-associated virus 6.2FF (AAV6.2FF)–mediated monoclonal antibody (mAb) expression protects mice from mouse-adapted Ebola virus (MA-EBOV) challenge 5 months after a single intramuscular injection.

AAV vectors were administered 140 days prior to intraperitoneal challenge with 1000 times the lethal dose (50%) of MA-EBOV.

Kaplan-Meyer survival plots of AAV6.2FF-2G4, AAV6.2FF-5D2, and AAV6.2FF-2G4/AAV6.2FF-5D2 cocktail (A) and averaged mouse group weights (B).



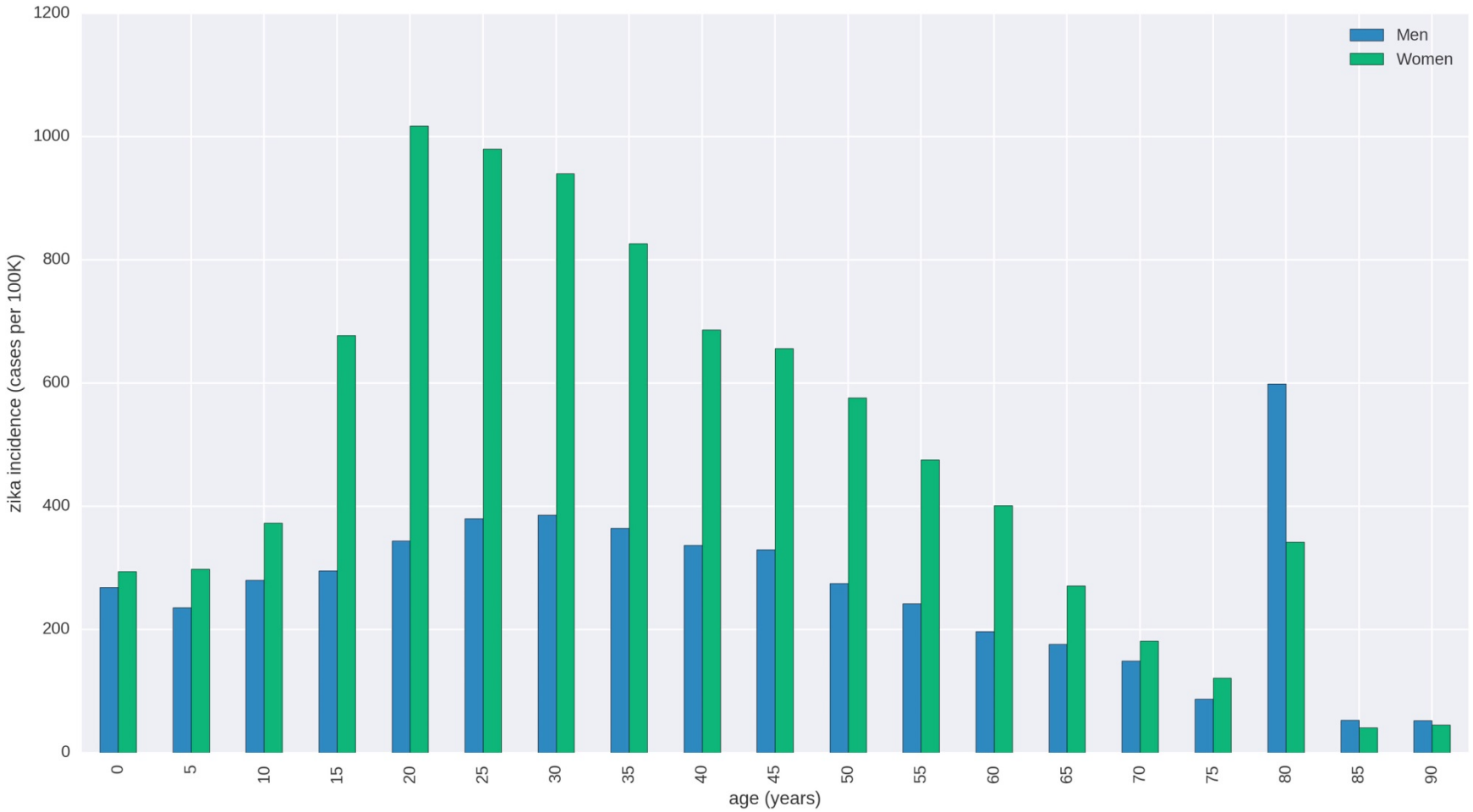
From: Intramuscular Adeno-Associated Virus–Mediated Expression of Monoclonal Antibodies Provides 100% Protection Against Ebola Virus Infection in Mice
J Infect Dis. Published online January 20, 2018. doi:10.1093/infdis/jix644

Zika

Can we infer the routes of infection transmission from incidence data?

- Higher incidence of Zika in adult women than adult men in Rio de Janeiro suggests a significant contribution of sexual transmission from men to women (Coelho *et al*. Int J Infectious Diseases October 2016)

Incidence of Zika in men and women by age group. The incidence is in units of cases per hundred thousand, Rio de Janeiro (Coelho *et al*. 2016)



International Journal of Infectious Diseases 2016 51, 128-132DOI: (10.1016/j.ijid.2016.08.023)

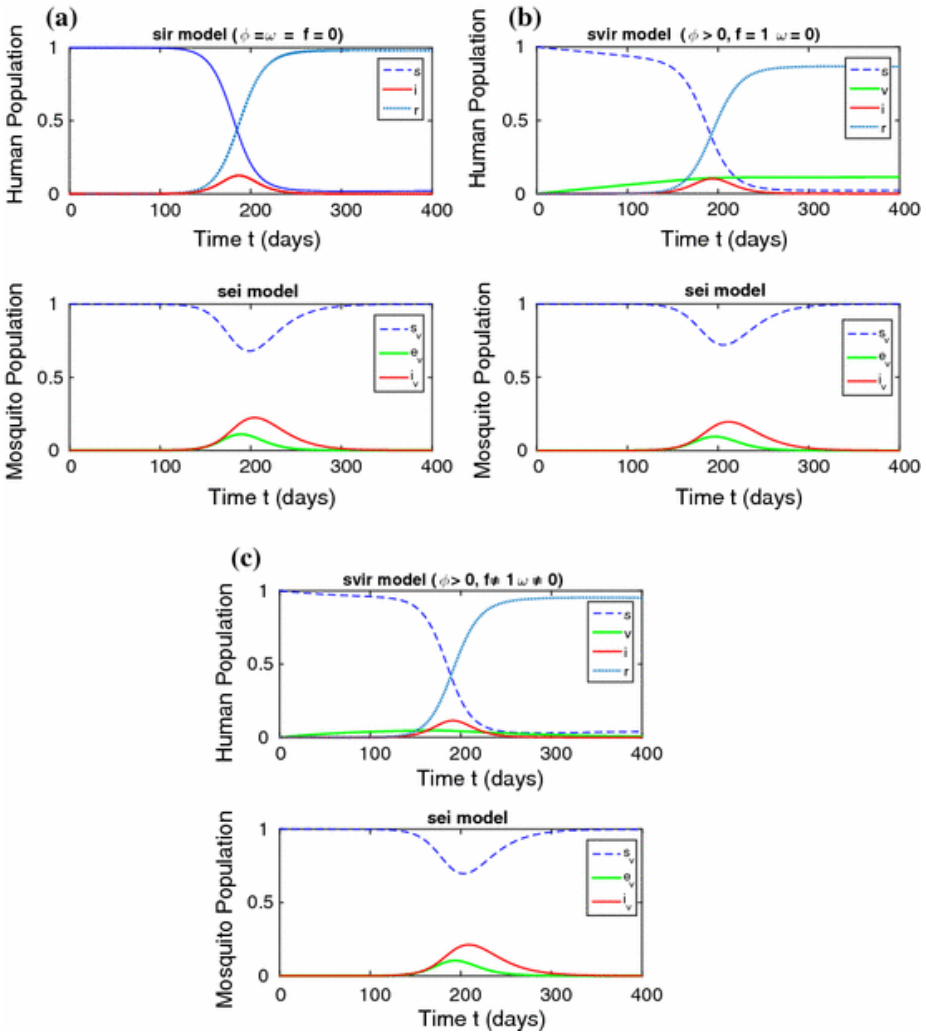
Zika transmission: sexual vs vector

- High levels of sexual transmission would create more cases of infection associated with the peak of infected humans arising in a shorter period of time, even when a vaccine were to be available

- However, a higher level of transmission of Zika from vectors to humans compared with sexual transmission implies that Zika virus would take longer to invade the population, providing a window of opportunities to control its spread, for instance, through vaccination

Valega-Mackenzie and Rios-Soto. Bulletin Mathematical Biology Jan 2018.
https://rd.springer.com/article/10.1007%2Fs11538-018-0393-7

Impact of vaccination on ZIKV spread. **a** Dynamics of ZIKV in the absence of vaccination infected humans. **b** Dynamics of ZIKV model under perfect vaccination rate. **c** Dynamics of ZIKV model with imperfect vaccination rate



Valega-Mackenzie and Rios-Soto. Bulletin Mathematical Biology Jan 2018. https://rd.springer.com/article/10.1007%2Fs11538-018-0393-7

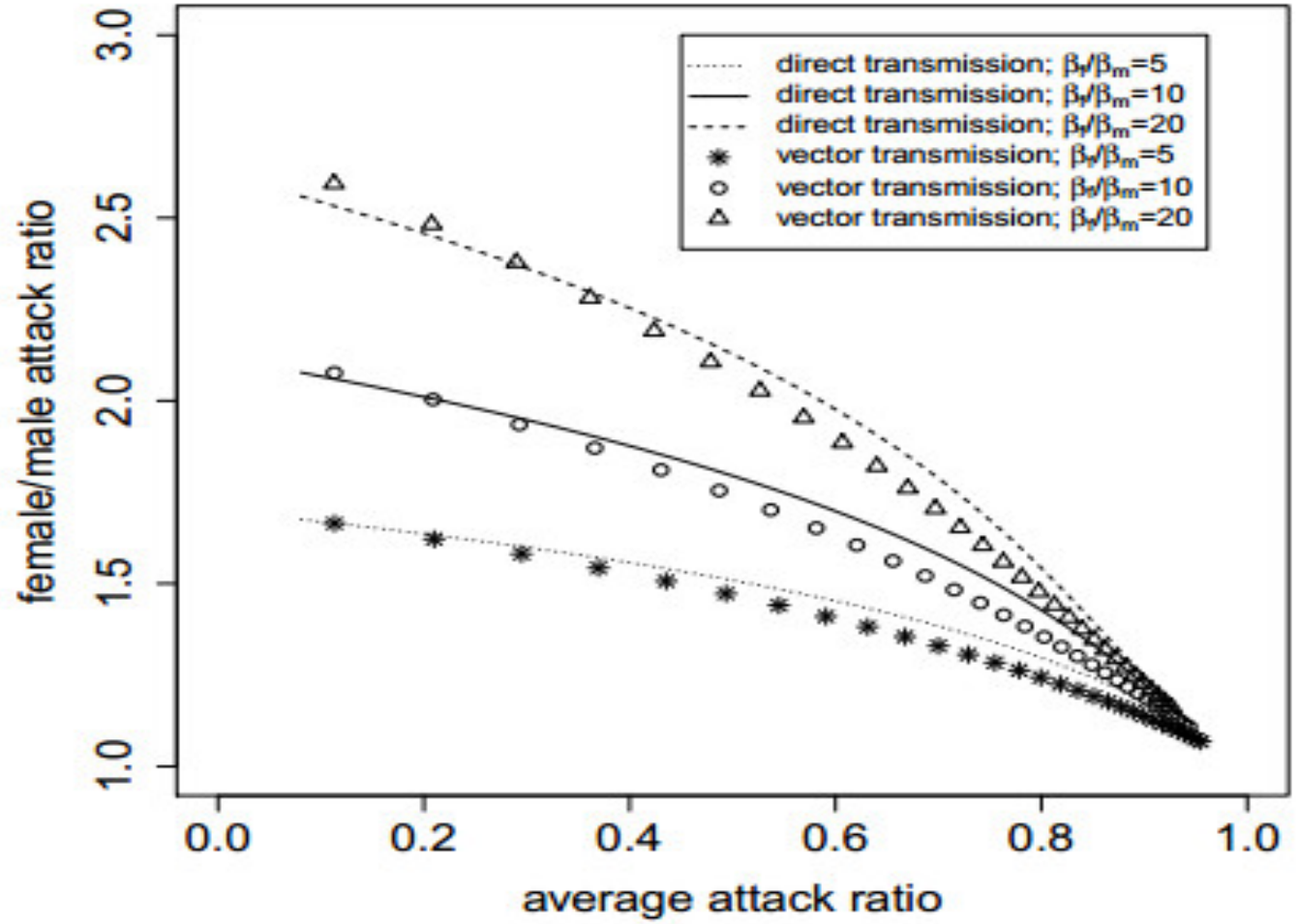
What can be inferred theoretically about the relevance of different transmission modes on unequal prevalence amongst the sexes?

- Andrea Pugliese, University of Trento, at the 9th Workshop Dynamical Systems Applied to Biology and Natural Sciences (DSABNS) 2018, Torino, Italy and Pugliese *et al*. Maths Biosci Eng 2018; 15(1): 125-140
  - Nothing so far in the literature, about the expected prevalence in the sexes for sexually transmitted diseases

http://dsabns2018.rd.ciencias.ulisboa.pt/

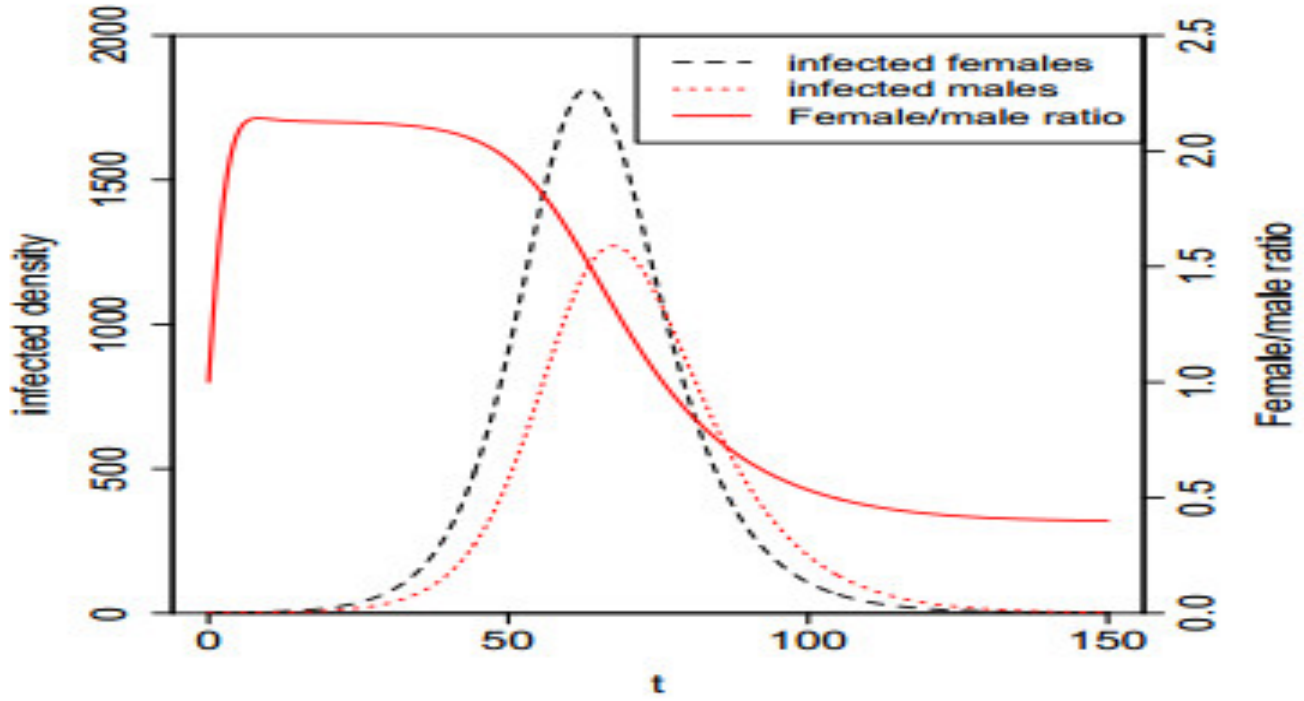
http://aimsciences.org/journals/displayArticlesnew.jsp?paperID=14139

Sex ratio of final attack ratios changes with average final attack ratio



Andrea Pugliese,Abba B. Gumel,Fabio A. Milner,Jorge X. Velasco-Hernandez. **Sex-biased prevalence in infections with heterosexual, direct, and vector-mediated transmission: a theoretical analysis.** Mathematical Biosciences & Engineering, 2018,15(1). http://dx.doi.org/10.3934/mbe.2018005

Examining the transient phase of the epidemic may yield a different picture: Initially, the sex ratio in new cases is closer to a value representing the ratio of susceptibilities, but then decreases because fewer susceptibles are left in that class. This simulation shows that even if the sex ratio of final attack ratios is 1.25, the ratio in new cases during the growing phase of the epidemic is around 2. Long dashed line (infected females); dotted line (infected males); solid line (ratio)



Andrea Pugliese,Abba B. Gumel,Fabio A. Milner,Jorge X. Velasco-Hernandez. **Sex-biased prevalence in infections with heterosexual, direct, and vector-mediated transmission: a theoretical analysis.** Mathematical Biosciences & Engineering, 2018,15(1). http://dx.doi.org/10.3934/mbe.2018005

WHO Zika Vaccine Tracker

Candidate	Platform	Immunogen	Adjuvant
GLS-5700	DNA	prME (pre-membrane and envelope)	None
AGS-v	Peptide	Mosquito salivary proteins	ISA-51
MV-Zika	Recomb. Viral vector	prME	None
mRNA-1325	mRNA	prME	None
VRC-ZKADNA085-00-VP and 090-00-VP	DNA	prME	None
ZIKV PIV	Inactivated whole target organism	Whole virus	Alum
PIZV or TAK-426	“	“	“

https://docs.google.com/spreadsheets/d/19otvINcayJURCMg76xWO4KvuyedYbMZDcXqbyJGdcZM/pubhtml#

Safety, tolerability, and immunogenicity of two Zika virus DNA vaccine candidates in healthy adults: randomised, open-label, Phase I clinical trials

- Study of two new DNA vaccines expressing pre-membrane and envelope Zika virus structural proteins
  - VRC5288 (in 18-35 year olds) n=80
  - VRC5283 (in 18-50 year olds) n=45
- Two Phase I randomised, open-label trials involving healthy adult volunteers
- Various schedules; follow-up for 24 months
- Both vaccines “safe and well-tolerated” – VRC5283 advanced to Phase II

Gaudinski *et al*. Lancet 4 December 2017

Yellow Fever

Yellow Fever

Chen and Hamer. Challenges in confronting the resurgent threat from Yellow Fever. JAMA 5 October 2017

- A new Yellow Fever (YF) outbreak commenced in Brazil in December 2016 (PAHO, 2017)
- The estimated risk of YF illness among travelers to Africa during epidemics is 50 per 100 000 persons for a 2-week stay, and for visitors to South America the risk is 5 per 100 000 persons (Staples *et al*. 2015)
- In 2015, the US Advisory Committee on Immunization Practices updated the YF vaccine recommendation to "a single primary dose of YF vaccine provides long-lasting protection for most travelers" (Staples *et al*. 2015)

PAHO. Epidemiological update: yellow fever, 10 July 2017. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=40841&lang=en

Staples *et al*. *MMWR Morb Mortal Wkly Rep*. 2015;64(23):647-650.

New Yellow Fever vaccine development

- Anticipated shortages of the traditional 17D vaccine because of the re-emergence of Yellow Fever
  - Live attenuated virus, developed in 1937, cultured in pathogen-free eggs
  - The original production seeds are “ageing past their peak”
  - Development of high volume production alternative to egg culture and generation of new sees
  - Development of inactivated vaccines

- RABYD-VAX consortium, University of Leuven hope to produce a cheap, efficient, temperature-stable and easy-to-produce vaccine against both rabies and Yellow Fever by 2020
  - Funded by the EU Horizon 2020 Programme

Pandemic influenza

Pandemic influenza vaccine development

- The mock-up procedure
  - Allows a vaccine to be developed and authorised **in advance of a pandemic**.
  - Mock-up vaccines contain a strain of flu virus that few people have been exposed to but that could potentially cause a pandemic
  - The vaccines are tested to determine whether they will protect people against the virus strain that they contain.

- Once the actual virus strain causing a pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for the vaccine to be authorised as a 'final' pandemic vaccine

- Four 'mock-up' vaccines are currently authorised in the EU. These can be modified into pandemic-influenza vaccines in a future pandemic

European Medicines Agency
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000462.jsp&mid=WC0b01ac058004b9ac

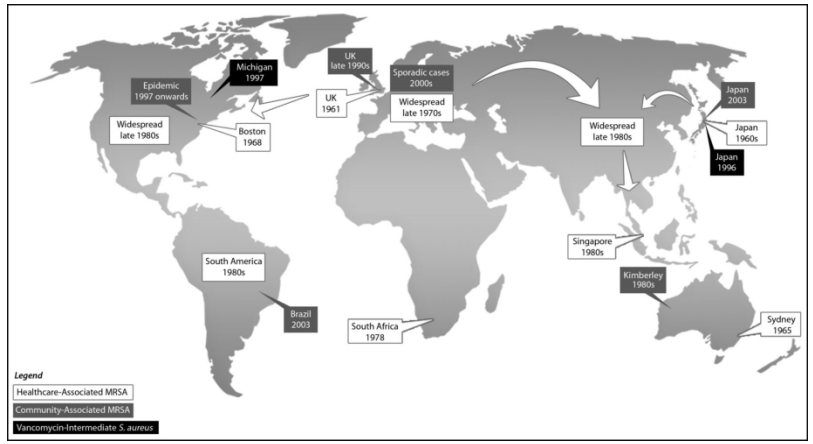
Mock-up vaccines authorised in the EU

- Daronrix – H5N1 whole virion, inactivated, adsorbed (lapsed marketing authorisation)
- Adjupanrix – H5N1 split virion, inactivated, adjuvanted
- Foclivia – H5N1 surface antigen, inactivated, adjuvanted
- Pandemic influenza vaccine H5N1 Baxter AG – whole virion, inactivated, prepared in cell culture
- Also two other procedures
  - The emergency procedure with fast-track approval
  - Modification of seasonal influenza vaccine

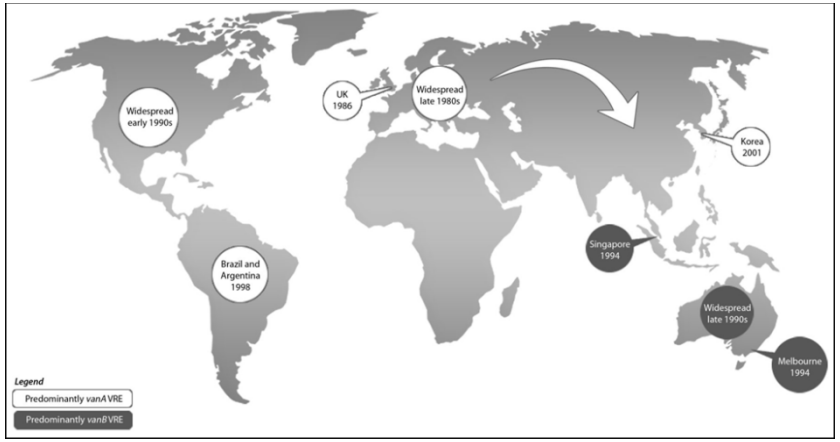
European Medicines Agency
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000462.jsp&mid=WC0b01ac058004b9ac

Resistant organisms

Global dissemination of multi-resistant organisms

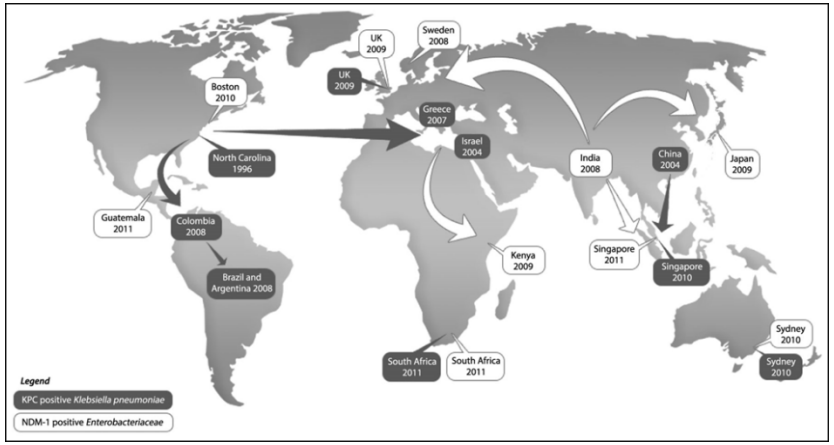


Methicillin-resistant
Staphylococcus aureus (MRSA)



Vancomycin-resistant Enterococcus (VRE)

Enterobacteriaceae: carbapenemase-producing *Klebsiella pneumoniae* and New Delhi metallo-β-producing Enterobacteriaceae



From: The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia
Clin Infect Dis. 2013;56(9):1310-1318. doi:10.1093/cid/cit020

WHO priority pathogens list for R&D of new *antibiotics*

- Priority 1: critical
  - *Acinetobacter baumannii*, carbapenem-resistant
  - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
- Priority 2: high
  - *Enterococcus faecium*, vancomycin-resistant
  - *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
  - *Campylobacter* spp., fluoroquinolone-resistant
  - *Salmonellae*, fluoroquinolone-resistant
  - *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant
- Priority 3: medium
  - *Streptococcus pneumoniae*, penicillin-non-susceptible
  - *Haemophilus influenzae*, ampicillin-resistant
  - *Shigella* spp., fluoroquinolone-resistant

http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

Prophylactic vaccine development for *Acinetobacter baumannii*

Candidate	Immunogenicity	Protection	Barriers
Glycoconjugate	Not possible – variability among glycan structures		
Inactivated whole cell	Highly immunogenic; elicits antibodies against multiple bacterial antigens	Protection of mice from multiple *A. baumannii* strains	High levels of lipopolysaccharide and difficulty in standardising the composition due to the high number of antigens
Outer membrane vesicles	"	"	
Individual bacterial components	Biofilm-associated protein Bap elicits high levels of antigen-specific titers	Reduced post-infection tissue bacterial loads: protects mice in intraperitoneal infection model	Yet to demonstrate in other models and in humans
	OmpA highly immunogenic in mice	Partial protection in mouse disseminated sepsis	

https://www.sciencedirect.com/science/article/pii/S0966842X12002259?via%3Dihub

Prophylactic vaccine development for *Pseudomonas aeruginosa*

	Immunogenicity	Protection	Barriers
LPS-based	For many O antigens, protective epitopes are poorly immunogenic	Some efficacy in adult cancer and burn patients	Limited by toxicity
Bivalent flagella		Reduction in infection in CF	Development ceased
Live-attenuated		Δ*aroA* protective against lethal pneumonia in mice	Absence of IL-17 receptor abrogates efficacy
Outer membrane proteins	Intranasal administration in mice elicits strong Th17 response	IL-17-dependent, ab-dependent protection from lethal pneumonia	

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521563/

Multi-drug resistant Gram negative rod vaccine design

Campfield *et al*. Curr Opin Immunol June 2014

- As Th17 cells confer serotype-independent immunity against heterologous infection, these cells likely recognise conserved antigens common among enterobacteriaciae family members

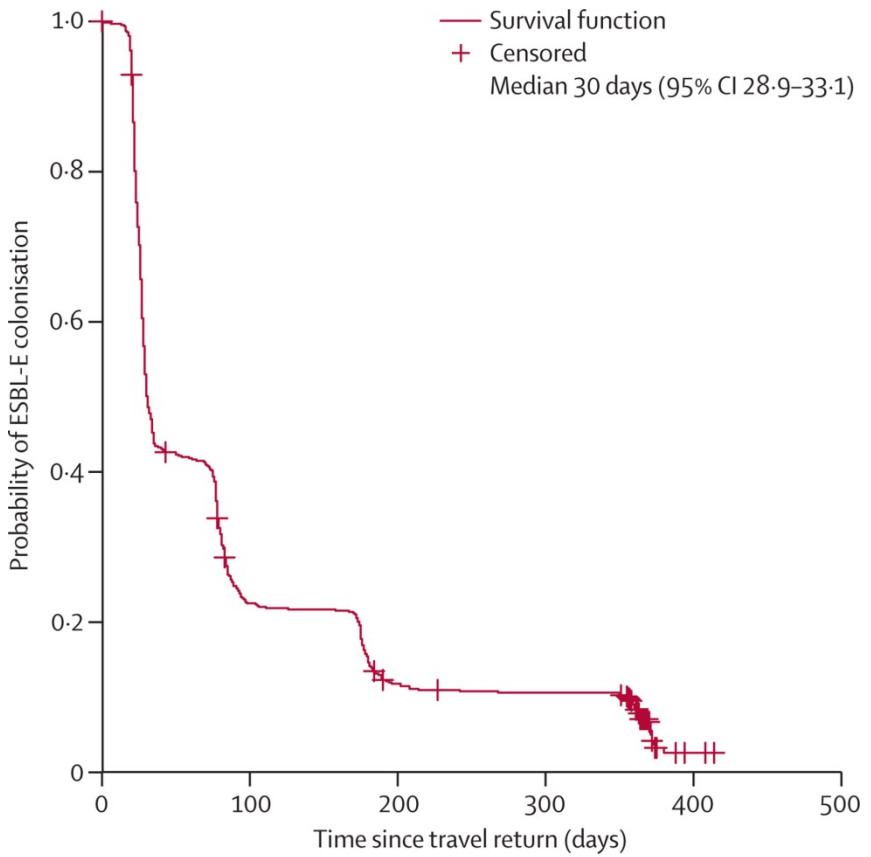
- One group of antigens recognized by Th17 cells are outer membrane proteins of *K. pneumoniae*, a group of proteins that are highly conserved among *Klebsiella* species, and the recognition of these antigens is highly dependent on MHC class II, suggesting that these proteins can be well defined and serve as antigen candidates for clinical translation

- Vaccination with purified outer membrane proteins of *K. pneumoniae* also elicits a strong Th17 response and provides heterologous protection against a broad spectrum of different strains including metallo-beta-lactamase 1 producing strains

- Another group of antigens include the machinery of the type 3 secretion system, such as the *Pseudomonas aeruginosa* PopB

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4037349/

Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): A prospective, multicentre cohort study
Arcilla *et al*. Lancet ID 2017; 17(1): 78-85



Kaplan-Meier estimate of time to decolonisation of ESBL-E in travellers

https://www.sciencedirect.com/science/article/pii/S147330991630319X?via%3Dihub

Multi-drug resistant Gram negative rod (GNR) vaccine design

Campfield *et al*. Curr Opin Immunol June 2014

- Route of administration must be an additional consideration in MDR GNR vaccine design
- As most pathogens access the body via mucous membranes, it is not surprising that mucosal immunisation is highly effective at inducing long-term B and T cell memory
- Pre-clinical models demonstrating Th17 mediated protection and the development of mucosa-associated lymphoid tissue (MALT) have employed intranasal and oral antigen immunization
- The immune responses induced by nasal delivery are usually highly robust and confer effective protection

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4037349/

Conclusions

Conclusions

- Viruses
  - BARDA funding for a range of filovirus vaccine development
  - Role for Zika vaccination in preventing spread by sexual transmission
  - Global shortages of Yellow Fever vaccine
  - EMA procedures for pandemic influenza vaccine
- Resistant organisms
  - Deeper understanding of immunology and transmission required
  - Determination of “best” route(s) of administration of vaccines
  - Role of vaccines in limiting global spread, for example, in travellers
- Preparedness
  - Establishment of collaboration and alignment across the disciplines covered by each of the preparedness networks, in order to bring European preparedness and response to the next level