New Vaccines Against Epidemic Infectious Diseases

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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

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
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Examples</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated virus and subunit vaccines</td>
<td>Classic subunit vaccines need improvement in immunogenicity; virus-like particle approach more promising</td>
<td></td>
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<tr>
<td>Non-replicating vaccine vectors</td>
<td>Alphavirus and flavivirus replicons</td>
<td>Use of Venezuelan equine encephalitis and Kunjin virus platforms</td>
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<tr>
<td></td>
<td>DNA vaccines</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Recombinant adenovirus-based vectors</td>
<td>First described in 2000. Problem of pre-existing immunity. Development progressing</td>
</tr>
<tr>
<td></td>
<td>Recombinant ZEBOVΔVP30</td>
<td>Through reverse genetics systems. 100% protection in guinea pigs</td>
</tr>
<tr>
<td>Replication-competent vaccine vectors</td>
<td>Recombinant vaccinia, CMV, paramyxovirus, rabies. vesicular stomatitis</td>
<td>Vesicular stomatitis rVSV-ZEBOV vaccine efficacious</td>
</tr>
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</table>
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)

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

The Lancet 2017 389, 505-518 DOI: (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).
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)
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.

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

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://aimsciences.org/journals/displayArticlesnew.jsp?paperID=14139
Sex ratio of final attack ratios changes with average final attack ratio

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.

# WHO Zika Vaccine Tracker

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Platform</th>
<th>Immunogen</th>
<th>Adjuvant</th>
</tr>
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<tbody>
<tr>
<td>GLS-5700</td>
<td>DNA</td>
<td>prME (pre-membrane and envelope)</td>
<td>None</td>
</tr>
<tr>
<td>AGS-v</td>
<td>Peptide</td>
<td>Mosquito salivary proteins</td>
<td>ISA-51</td>
</tr>
<tr>
<td>MV-Zika</td>
<td>Recomb. Viral vector</td>
<td>prME</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1325</td>
<td>mRNA</td>
<td>prME</td>
<td>None</td>
</tr>
<tr>
<td>VRC-ZKADNA085-00-VP and 090-00-VP</td>
<td>DNA</td>
<td>prME</td>
<td>None</td>
</tr>
<tr>
<td>ZIKV PIV</td>
<td>Inactivated whole target organism</td>
<td>Whole virus</td>
<td>Alum</td>
</tr>
<tr>
<td>PIZV or TAK-426</td>
<td>“</td>
<td>“</td>
<td>“</td>
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[https://docs.google.com/spreadsheets/d/19otvINcayJURCMg76xWO4KvuyedYbMZDcXqbyJGdcZM/pubhtml#](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
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)


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
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
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

Prophylactic vaccine development for *Acinetobacter baumannii*

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

<table>
<thead>
<tr>
<th>Immunogenicity</th>
<th>Protection</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS-based</td>
<td>For many O antigens, protective epitopes are poorly immunogenic</td>
<td>Some efficacy in adult cancer and burn patients</td>
</tr>
<tr>
<td>Bivalent flagella</td>
<td>Reduction in infection in CF</td>
<td>Development ceased</td>
</tr>
<tr>
<td>Live-attenuated</td>
<td>ΔaroA protective against lethal pneumonia in mice</td>
<td>Absence of IL-17 receptor abrogates efficacy</td>
</tr>
<tr>
<td>Outer membrane proteins</td>
<td>Intranasal administration in mice elicits strong Th17 response</td>
<td>IL-17-dependent, ab-dependent protection from lethal pneumonia</td>
</tr>
</tbody>
</table>

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521563/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4521563/)
• As Th17 cells confer serotype-independent immunity against heterologous infection, these cells likely recognise conserved antigens common among enterobacteriaceae 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

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