IHTM

Vaccinology Problem-Based Learning Project

Hilary Term 2024

Aim

The aim of the PBL is to give students a project where they can apply the concepts learned in the sessions to tackling a global real-world challenge. The project will require integration of the technical knowledge, public and global health applications, and policy and ethical considerations in vaccinology. The aim is to encourage critical appraisal of evidence from diverse sources, engagement with experts from different spheres, and a deeper understanding of how the technical and public health themes of the vaccinology module influence each other in the real world.

The students will have support to write up their PBL projects as a commentary piece and submit it for publication if they choose to do so, completing this in their own time.

Structure

1. Introduction to the problem

At the start of the module, students will be divided into two groups (combining IHTM and auditing students) and given their project scenarios. The groups, in coordination with each other, will work on this over the next month, with touch points to keep the process turning over from halfway through the module.

Background to the problem scenario

Influenza is a contagious respiratory illness that infects millions of people each year through seasonal outbreaks. Its impact ranges from mild to severe, causing substantial morbidity and mortality worldwide (according to the WHO, about 290,000 to 650,000 deaths per year). Vaccines are one of the primary defence mechanisms in the public health response to influenza. However, influenza vaccines face challenges in sustaining efficacy, primarily due to rapid and continual antigenic drift. This phenomenon necessitates annual updates to vaccine composition, a process that relies heavily on predictions, which can become out-of-date during the process of vaccine production.

Additionally, there is potential for severe influenza pandemics due to antigenic shift or reassortment of genes from influenza viruses that affect different species. This antigenic shift can affect both the pathogenicity and transmissibility of the virus, leading to the emergence of novel, more virulent strains against which humans have little to no pre-existing immunity and which can spread quickly through naïve and susceptible human populations. The four pandemics of the last century (1918, 1957, 1968, and 2009) caused more than 50 million deaths. The most likely next global pandemic will be influenza.

Despite its prevalence and potential to cause severe pandemics, influenza often remains a low priority for both individuals and governments, overshadowed by health concerns deemed more pressing. This can lead to gaps in surveillance, preparedness, and response, leaving populations vulnerable to outbreaks. However, the global health community's experience with the COVID-19 pandemic has brought renewed attention to the importance of robust pandemic preparedness. Lessons learned

from the recent pandemic, alongside new advances in technological platforms, big data analytics for disease surveillance and global information sharing, present new opportunities to address some of the public health challenges in dealing with both seasonal and pandemic influenza.

2. Group projects

1) Group 1: Technical challenges
    a. **Role: you are members of an advisory group to a major global funding body**
    b. **Your task:** you have been tasked to critically appraise the current influenza vaccine landscape and make recommendations of where this funder should invest to improve seasonal vaccine performance while speeding development of a highly efficacious, universal influenza vaccine.
    c. **Some guiding questions** to consider in building your recommendations:
        i. What is the life cycle of influenza within the human body and across the population (e.g., because of original antigenic sin and the immunological legacy of prior exposures to influenza) and how does this affect the efficacy of influenza vaccines and of vaccination strategies?
        ii. What ways might there be to improve on the narrow and short-lived efficacy of current seasonal flu vaccines and the long lead times between choices of strains and delivery of vaccines which can also mean they have lower efficacy than originally planned?
        iii. In years when efficacy, in terms of preventing infection, is low (as low as 10%, compared to about 55%-60% in healthy adults when vaccine viruses are well matched to circulating strains), what use is mass influenza vaccination? (bearing in mind the impact of other respiratory infections which can coinfect during influenza, the need to counter antimicrobial resistance, and health care system impacts).
        iv. In general, what assumptions are we making about the impact of repeated vaccinations on the immune response that we might want to factor into our investment recommendations? E.g., given immune biases caused by prior influenza virus infections reducing vaccine efficacy in some influenza virus seasons, and given that repeated vaccination can lead to diminished B cell responses and faster postvaccination antibody waning, could vaccination strategies be modified (e.g., more targeted and less mass use, or changing of strains, etc.) or vaccines be improved?
        v. What is the current landscape of influenza vaccines?
            1. What is the nature of the current vaccine technology and how is this circumvented by evolution of the influenza virus
            2. How might funding be reconfigured to improve the probability of protection from seasonal vaccines and the chances of developing a universal influenza vaccine (say, by targeting the conserved stalk or stem of the HA, and the M2 protein, and not just the continuously evolving global head domain of the HA)?
            3. What if universal influenza vaccines also only provide short-term efficacy?
            4. What are the existing challenges to research and development? This might cover trials, regulation and safety, how exposure over lifetime to influenza antigens shapes host response to influenza virus infection and vaccination and hence ‘vaccine efficacy’, etc.

vi. As a way to address current challenges, what is the potential for, and challenges/limitations of, 'newer' technologies, like mRNA, oral tablet-based or nasal spray-administered vaccines versus intramuscular injections, next-generation adjuvants, alternatives to egg-based production, etc.? For example, even if mRNA reduces costs of manufacture, maximum possible dose (because of adverse reactions) might limit the number of antigens covered with many below the threshold needed for protection unless the technology can be improved to operate with much lower doses.

vii. Could 'older', immediately implementable, technologies be improved, for example by next-generation adjuvants or viral vectors acting as adjuvants, or improved vaccine strain antigenic match based on better surveillance, antigenic data, antigenic cartography, predictive evolution and viral forecasting models, and AI-driven epidemiology, or better (though very challenging to establish) correlates of protection, or different vaccine platforms used in prime/boost strategies, etc.? What roadblocks (e.g., regulatory, economic, political) would need to be tackled?

viii. What is the appropriate balance between investing in seasonal and universal vaccines given all the uncertainties and risks? Since fatalities in interpandemic periods are at least equivalent in scale to those caused by pandemics, there seems to be some logic in connecting investments across the different horizons.

ix. What business model shake-up might be needed? The current system is cumbersome and elaborate but, after 70 years, well entrenched. It produces only a few hundred million doses a year for a profitable $1.6billion US market and a $4billion global market. Displacing a familiar, well-oiled machine with new and potentially improved vaccines is challenging (e.g., placebo-controlled trials of new technologies are difficult to justify in markets with already licensed vaccines; giving experimental vaccines in addition to conventional seasonal vaccines and trying to measure improved efficacy when circulating vaccines are mismatched with the seasonal vaccine will need large, complicated, costly, and unpredictable trials; and human influenza challenge models are no panacea either).

2) Group 2: Preparing for a Global Influenza Pandemic
   a. **Role: you are a think tank advising the UK government**
   b. **Your task:** you have been tasked to set up a series of war game scenarios for a global influenza pandemic. Make reasonable and justifiable assumptions on the available technologies, manufacturing processes, political climate, vaccine hesitancy, etc. at the time. Outline critical decision points and give recommendations on the priorities for a response.
      i. The first scenario is that a global influenza pandemic is currently in its early stages. There are a growing number of cases across the world, with transmission rates similar to the 2009-2010 H1N1 outbreak but greater severity and mortality rates. You have current levels of preparedness and technology with the ability to implement technologies that are currently tested but not yet in wide circulation.

ii. The second scenario is that a global pandemic starts in January 2035, with transmission rates similar to the 2009-2010 H1N1 outbreak but greater severity and mortality rates, and you have ability to change the level of preparedness and available technologies.

c. **Some guiding questions** to consider in building your recommendations:
   i. What if an influenza virus emerges from birds and is pathogenic for poultry and gains the ability to easily transmit between humans who have no immunity against such a new animal-origin virus, and we are still reliant on embryonated egg-based approaches to develop and produce vaccines to tackle the virus? The egg-based approach builds in long production schedules by default, and egg-adapted mutations during that process can weaken protection from the vaccines produced. How quickly could alternatives be deployed (e.g., based on insect cells, DNA vaccines, virus-like particles, mRNA, etc.), and what would be the major limiting factors?
   ii. What are the major challenges to developing and implementing vaccines at scale? (technical, manufacture, supply, contextual, ethical, etc.)
   iii. What are the global power dynamics that would need to be considered and how would you address them? What major tensions between diverse political systems that would need to be weighed up?
   iv. In what ways has the ability to respond improved, or not, on account of the recent COVID-19 pandemic? Most people experience influenza-like illnesses regularly, but actual influenza only about once per decade. Are there non-vaccine ways to respond to an influenza pandemic the efficacy of which have been highlighted by COVID-19 evidence (e.g., hand washing, PPE, staying at home when ill, etc.)? Have detection mechanisms improved enough to help speed pandemic flu responses, especially to develop, manufacture, and globally deliver vaccines matching the pandemic strain?
   v. What are the populations at risk? What is the impact of the recent pandemic on population vulnerabilities? For example, since childhood exposure in particular affects vaccine efficacy against seasonal influenza virus, what might be the consequences of both seasonal and pandemic influenza in populations impacted by COVID-19 and recent lockdowns? Are outbreaks of respiratory disease in children in northern China a hint of things to come? What about older populations and those vulnerable to complications of severe influenza?
   vi. The response to the 2009 global influenza pandemic was held back by the difficulty in producing and distributing enough vaccines to prevent the second wave. As a way of avoiding such a future predicament what are the pros and cons of stockpiling vaccine seed viruses against subtypes deemed of pandemic potential, of testing candidate vaccines in advance in preclinical studies and clinical trials, and of setting up new vaccine technology platforms?
   vii. How might we improve collaborations between global stakeholders including funders, basic scientists, regulators, vaccine developers and manufacturers, and global health agencies so that the global response is better than it was against COVID-19? How in particular might healthcare resources be ethically distributed and, in particular, vaccines equitably developed and delivered?
   viii. How do the two scenarios (an imminent global influenza pandemic and a pandemic in 2035)compare? What current investment and technology strategies will lead the world to being better vaccine-prepared in 2035? Are

there any low-hanging investment fruits and what are the more challenging investments? Who should pay?

3. Group members

Each group is made up of IHTM students who have chosen to take the vaccinology module (full or auditing) as well as DPhil students auditing the module.

Group 1: names removed for publicly available file

Group 2: names removed for publicly available file

Work on the PBL project will take place out of class time, with division of labour organised by the students.

4. Support through the module

Three or four 60-minute sessions will be organised with guest experts, from midway through the module. The purpose of these sessions is to:

- Allow a space for students to ask experts questions, sense-check their ideas and develop their thinking in relation to their approach to their group's PBL project
- Give the students exposure to a range of inputs and expert opinions
- Encourage steady progress on the PBL project

Students will send a list of 3-5 questions to the course coordinator and PBL-lead 2 days in advance of each session for input.

Format (online)

1. Introduction to the guest expert and to the PBL problem: 5 minutes
2. Both Groups get the floor for 20 minutes each to ask any burning questions – the responsibility is on the students to come with questions, not on the experts to lecture.
3. Wrap up: 5 minutes

Proposed guest experts:

- Technology platform expert (e.g., mRNA)
- Safety/regulation expert
- Public health specialist
- Supply chain specialist
- Expert from international organisation, probably WHO

Outputs

The PBL projects will be presented to a panel on the 12th March 2024. Each group will present for 20-30 minutes, followed by 15 minutes of clarifying questions. A panel discussion between the expert panellists will follow, triggered by the concepts and questions raised by the presentations.

If the students choose to do so, they will be supported to collate the project work into a commentary piece that can be submitted for peer review. Feedback from the PBL presentation can be incorporated, and the groups can combine their work or write separate pieces. All manuscripts will be submitted using the "green" open access route with self-archiving of the author accepted manuscript, unless the chosen journal agrees to waive the article processing charges. There is no guarantee that the piece will be published as it will go through the usual peer-review process. Support will be available from the module coordinator until the end of September 2024.