Society of Actuaries in Ireland

Prospects for Covid-19 Medicines

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Disclaimer

The views expressed in this presentation are those of the presenter and not necessarily those of the Society of Actuaries in Ireland.

Agenda

1. Short biotech primer
2. Prospects for vaccines
3. Prospects for antivirals
4. Prospects for antibodies
5. Prospects for ‘repurposed’ drugs
6. Future Scenarios & Conclusion

1. Short Biotech Primer

Developing a Novel Drug (Vaccine as example)

- Pre-clinical
  - Develop & refine a prototype
  - Test on blood/tissue samples
  - Test on animals

- Phase I (c.25-75 Fit & Healthy Adults)
  - Escalating drug doses in sequential manner
  - Goal = High-level safety & hints of effectiveness

Developing a Novel Drug (Vaccine as example)

- Phase II (c.200-500 Healthy Adults)
  - Test doses & placebo in parallel manner
  - Goals = safety & level of antibody response
  - Company = controls trial design, conduct & analysis

- Phase III (c.40,000+ Average Adults)
  - 2 similar trials done in parallel
  - Goals = establish vaccine effectiveness & detailed safety
  - Regulator = controls trial design, conduct & analysis

- Regulatory Approval
  - Key regulators are US's FDA and EU's EMA

1st Phase III Trial for Zostavax Shingles Vaccine

Trial Arm	Lives Included (aged 50-59)	Shingles Cases	Incident Rate (per 1,000 exposure years)
Zostavax Vaccine	11,211	30	1.994
Placebo Injection	11,228	99	6.596

- Vaccine **70%** effective (i.e. 1 – 1.994/6.596)
- Lives tracked for 1.3 years to accrue cases (plus time to enrol)
- Highlights key facets of Phase III vaccine trials
  - No vaccine is 100% effective
  - Thousands of lives needed to accrue required infections
  - Requires time to accrue infections
  - Pathogen must be actively circulating during the trial

Infectious Disease Medicine Development

Stage	Nominal Probability Of Approval	Adjusted Covid-19 Probability Of Approval	Average Stage Duration
Phase I	20%	31%	1.5 years
Phase II	31%	42%	2.0 years
Phase III	65%	69%	2.3 years
Regulatory Approval	88%	94%	1.3 years

- Adjustments to nominal probabilities
  - c.25% Phase I & II stop for ‘non-scientific’ reasons - assume doesn’t apply here
  - Regulators accommodative for Covid-19
- Speed up by doing work in parallel, quick enrolment & just 1 Phase III
- Approval has a high bar on safety & a low bar on efficacy
  - One third of all drug launches are commercial failures

2. Prospects for Vaccines

Vaccines - Introduction

- 70+ vaccines in development
  - 5 discussed in Appendix A
- Pre-clinical & Phase I reports suggests multiple vaccines have promise
- Covid-19 not intrinsically difficult to produce a vaccine for
  - Coronavirus vaccines successfully developed for animals
  - Unlike HIV, Hepatitis C and HSV where all vaccines have failed
- I have no doubt multiple vaccines will be speedily developed
- However, valid concerns about
  - Scaling up manufacturing
  - Issues with the elderly and children
  - Difficulty in achieving ‘herd immunity’

Subunit Vaccines

Uses a distinctive pathogen fragment that immune system develops antibodies against. Fragments are currently manufactured through complicated fermentation. Most modern vaccines are of this type.

- Pros
  - Adjuvants boost effectiveness & lower dosage levels
  - Safer than traditional vaccines (critical if skipping safety work here)
  - Work even if immune system weakened
- Cons
  - Time consuming to design
  - Still moving from low yield & slow to scale up manufacturing (e.g. popular Gardasil vaccine for HPV current capacity is <c.50m doses) to next gen. with high yields & quick to scale up

RNA/DNA Vaccines

Uses DNA (or RNA) that codes for a distinctive pathogen subunit. Enters into person's cells using a 'vector' – often an altered (harmless) virus – where gets translated into many copies of the desired subunit.

- Pros
  - Small dose amounts allow for huge production runs
  - Design process is quick
- Cons
  - None has yet been approved by regulators
  - None has yet passed a full Phase III trial
  - None has yet been produced at commercial scale
  - Don't readily have their potency boosted by adjuvants

Vaccines Issues – The Elderly

Age Band	Zostavax Shingles Vaccine Effectiveness	Shingrix Shingles Vaccine Effectiveness
50 – 59	70%	97%
60 – 69	64%	97%
70 – 79	41%	91%
80+	18%	91%

- Immune system declines with age & impairs vaccine effectiveness
- Can counter through effective vaccine design
  - Zostavax (2006) = 'Traditional' 1-dose modified virus vaccine with no adjuvant
  - Shingrix (2017) = 'Modern' 2-dose subunit vaccine with superlative adjuvant
- Similar age-related trends apparent with influenza vaccines
- Strategically concerning problems
  - Elderly most vulnerable to Covid-19
  - Undermines population-wide herd immunity
  - A Shingrix-like solution will likely be slow to develop & hard to make

Vaccine Issues – Children

- Covid-19 vaccine trials only using adults
- Only after launch will trials begin on children
  - May have to lower the dose or adjust the injection schedule
- Strategically concerning problems
  - Standard safety tests are being skipped
  - Phase III trials may be truncated or bypassed completely
  - Children least affected by Covid-19
- Take-up could then be disappointing
  - Regulators may not recommend initial use on children
  - Parents may not consent without full & complete safety data
- Many vaccines don’t work on infants

Vaccine Issues - Manufacturing

- Target is world population of c.7.8bn people
- Influenza vaccines the biggest seller
  - Yearly capacity = c.1.5bn people (versus <0.15bn for a childhood vaccine)
  - Made across c.35 plants
- Risk secondary pandemics if existing plants commandeered
- Several pivotal manufacturing binaries
  - Will DNA/RNA & ‘next gen.’ subunit vaccines deliver promised quantum leap?
  - Will a 1 or 2 dose vaccine regime be needed for non-elderly lives?
  - Will effectiveness last more than 2-3 years?
  - Will large vaccine doses be required?
- Biggest bottleneck could be skilled people – not money, red tape or construction

Issues on Vaccine Phase III Trials

- Skip altogether to save time?
  - Need to determine best-performing vaccines
  - Safety data on broad cross-section of population
  - Manufacturing ramping up H2 20 to H2 21 so window exists
- Run as ‘virus challenge’ trials to save time?
  - Not tenable for older lives – which vaccine should they then get?
  - Misleading outcomes – challenge level may not match real-world
- WHO proposed multi-drug Phase III trial a good model
  - Efficient as just 1 placebo arm compared to several vaccines
  - Quick enrolment as low chance of getting a placebo
  - No need for 2nd Phase III trial
  - Definitive effectiveness comparison between vaccines

4. Prospects for Antivirals

Antivirals - Background

- Directly attack the virus (independent of immune system)
- Manufacturing quick & highly scalable
- Effective at controlling HIV and curing Hepatitis C
  - Approaches used there not effective against Covid-19
- Antiviral effectiveness against influenza is likely a better guide…

Influenza Antiviral	Format	Improvement in Recovery Time	Mortality Benefit	Prevention Effectiveness
Rapivab	Injection	0.9 days	None	Not practical
Relenza	Inhalation	1.2 days	None	67%-86%
Tamiflu	Tablet	1.3 days	None	75%-94%
Xofluza	Tablet	1.1 days	None	86%

- Must take within 2 days of symptoms emerging
- Prevention requires prior daily dosing & only tablets/inhalation practical

Antivirals - Remdesivir Class

- Developed for Ebola & moderately effective
- Ebola & covid-19 are the same type of single-stranded RNA virus
- Large Phase III trials under way
  - Reduced recovery time by 4 days (good for hospital capacity)
  - Reduced mortality from 11.6% to 8.0% (not statistically significant)
- Only dosable through I.V. drip
  - Preventative use impractical
- Galidesivir is the only other antiviral similar to Remdesivir
  - Currently in Phase I (I.V. drip format)
  - Critically, its chemistry allows tablet dosing
- No other current antivirals show promise
  - 4-5 years to launch new antiviral classes from scratch

4. Prospects for Antibodies

Antibodies

- Vaccines' purpose is to induce immune system to make antibodies
- Other ways to generate antibodies
- Firstly, precedent with RSV (influenza-like virus)
  - Synagis approved in 1998 to treat RSV in children (no successful vaccine exists)
  - Consists of engineered antibodies grown in fermentation factories
  - Monthly injections to high-risk children during winter seasonal peak
  - 45%-55% effective against RSV infection
- Secondly, precedents with Ebola
  - mAB114 & REGN-EB3 are engineered Ebola antibodies
  - In Phase III, reduced mortality to c.30% (c.50% in control arms)
  - Promptly treated patients had c.10% mortality

Antibodies

- Thirdly, ‘convalescent plasma’ is well-established strategy
  - Transfuse plasma from recovered patients (with antibodies) to those currently ill
  - Small trials indicate benefits in Covid-19 & large trials under way
  - Prudent to prepare national blood-collection systems to collect donations

- Fourthly, several Covid-19 engineered antibodies in development
  - Clinical trials are due to begin in ‘late summer 2020’
  - May jump straight to Phase II (risk/benefit tolerant for sick patients)

5. Prospects for ‘Repurposing’ Medicines

Repurposing Medicines (CRS)

- Covid-19 could be viewed as 2 distinct diseases: viral infection & CRS
- CRS = Cytokine Release Syndrome (severe/lethal immune system over-response)
- CRS causing many lung-related Covid-19 deaths
- IL-6 Inhibitors (Actemra, Kevzara & Sylvant)
  - IL-6 immune system component is key to CRS in Covid-19
  - 3 IL-6 drugs already exist (mainly used for rheumatoid arthritis)
  - The remaining immune system can still fight the virus
  - Initial Phase III trial suggests only effective for critically ill (e.g. on ventilator)
- BTK Inhibitor (Calquence) & JAK Inhibitor (Jakafi)
  - BTK & JAK drugs both used to treat ‘blood’ cancers (cancerous immune system elements)
  - Both have evidence of reducing CRS in Covid-19
  - First non IL-6 drugs ‘big pharma’ have touted for Covid-19

Repurposing Medicines (Viral Infection)

- Only aware of 3 drugs repurposed for viral infections
  - AZT (failed cancer drug) was the first drug approved for HIV
  - HIV antivirals have moderate effectiveness against Hepatitis B
  - Interferon also has moderate effectiveness against Hepatitis D
- Many existing drugs have been touted for Covid-19
- To date, many trials have been of disappointing credibility
  - Didn't have proper placebo arm (esp. given covid-19's high natural recovery rate)
  - Published reports reveal flaws in procedures & analyses
  - Run in 1-2 hospitals (best practice is to run across dozens of hospitals)
  - Few have had regulator input into trial design & management
  - Side effects may outweigh their, at best, moderate benefits
  - Selection bias as trials purporting to show benefits more likely to submit for publication, get published and gain publicity

6. Future Scenarios & Conclusion

Possible Vaccine Roll-Out Strategy

- Stage 1
  - Haven't completed Phase III trials
  - Low production – manufacturing only ramping up
  - Risk, benefit & capacity considerations pivotal
- Stage 2
  - Multiple safe, effective, 1 dose vaccines
  - High production - manufacturing scaled up
  - Give to whole population – adults, the elderly and children
- Stage 3
  - Potent Shingrix-class vaccine (likely 2 dose) that performs well with the elderly
  - Constrained production – complex manufacturing
  - Revaccinate everyone aged 60+ (c. 1 billion people)

‘Stage 1’ Rollout – Who Gets It?

- Regulators have already said health workers will be first
  - Risk/benefit supports first use here

- Implement a ‘ring’ treatment strategy
  - Everyone in contact with someone infected is immediately vaccinated
  - Everyone in contact with this group are also vaccinated
  - Virus trapped in a double-layered, protected ring
  - Successfully used with Ebola & smallpox 1970’s eradication campaigns
  - Important ‘carrot’ to add to testing & tracing

- Debate needed on care homes
  - Both benefit & risk (immature safety profile) are elevated

Timeline : Vaccine Rollout (Very Speculative Scenarios)

Milestone	'Everything Goes Right'	'Majority Goes Right'	'Manufacturing Struggles'
Start – Stage 1	Q4 20	Q1 21	Q2 21
Start – Stage 2	Q3 21	Q1 22	Q1 22
Start – Stage 3	H1 22	H2 22	H2 22
Finish – Stage 2	Q3 23	Q3 24	H1 26
Finish – Stage 3	H2 23	H1 25	H1 26
Stage 2 – Doses Run Rate	c.325m per month	c.260m per month	c.160m per month
Stage 3 – Doses Run Rate	c.110m per month	c.70m per month	c.50m per month

- Sense check: 3rd Scenario (Stages 2&3) = 210m doses per month
  - >1.5 x run-rate of c.35 mature influenza vaccine plants
- Equitable worldwide distribution assumed
  - If 2nd/3rd scenarios crystallise, developed countries may favour their own citizens

Vaccination – Population Herd Immunity Scenarios

Country	Stage 2 Only No Children	Stage 2 Only Half Children	Stage 2 Only All Children	Stages 2 & 3 No Children	Stages 2 & 3 Half Children	Stages 2 & 3 All Children
Ireland	54%	60%	67%	64%	71%	77%
Italy	56%	60%	64%	70%	74%	79%
Japan	54%	58%	63%	70%	75%	79%
Nigeria	42%	55%	69%	46%	60%	73%
UK	54%	60%	66%	66%	72%	78%
USA	54%	60%	66%	65%	71%	78%

- Assumptions in Appendix B (Red = No, Yellow = Maybe & Green = Yes)
- Scenarios imply full children take-up & ‘Stage 3’ vaccine needed
- Developing countries require confidence in vaccinating children

What if Vaccination Can't Provide Full Herd Immunity?

- Vaccines reduce illness severity in addition to help preventing illness

- Sample Spanish hospital influenza study…

Status	Number	% > age 65	% in ICU	CRS in Lungs	Organ Failure	Pneumonia
Vaccinated	450	84%	24%	32%	9%	70%
Unvaccinated	1,261	42%	38%	41%	11%	76%

- Infections required to bridge the gap – vaccines & medicines will lower mortality

- Need to establish covid-19 illness reduction in Phase III vaccine trials

Timeline & Success Estimates: Non Vaccine Medicines

Medicine	Results of Phase II/III trials	Regulatory Success Estimate	Mortality Signal Estimate	Medicine Widely Available
Remdesivir	Q2/Q3 20	Yes!	Yes!	Q3 20
Actemra (IL-6)	Q3 20	50%	25%	Q3/Q4 20
Convalescent Plasma	Q3/Q4 20	60%	25%	Q3/Q4 20
Calquence (BTK)	Q4 20	40%	25%	Q4 20
Jakafi (JAK)	Q4 20	40%	25%	Q4 20
Engineered Antibody	Q4/Q1 20/21(?)	70%	50%	Q3/Q4 21(?)

- Trials statistically sized to prove regulatory benefits
  - e.g. time to recovery or % entering ICU
  - Likely undersized to prove mortality benefits – but clear signals possible

- If several demonstrate benefits, the cumulative impact could be substantive

Strides in Viral Science Over Past 5 Years

- Shingrix adjuvant not yet vindicated by its Phase III trials
- RNA vaccines very experimental & not started in trials
- DNA vaccines still novel & not started in mainstream trials
- Large vaccine players not interested in RNA or DNA vaccines
- Next gen. subunit vaccine manufacturing still experimental & unproven
- Remdesivir yet to show efficacy against Ebola and similar viruses
- Using engineered antibodies to treat Ebola had not happened
- 1 out of 6 currently approved JAK drugs then launched
- 1 out of 3 currently approved IL-6 drugs then launched
- 1 out of 3 currently approved BTK drugs then launched

Thoughts on Science and the Recovery

- Recovery a journey of many steps, not a one-off binary
- Hope is powerful – recovery may front-run the science in some areas
- Some current changes will be permanent – with many for the better
- Speculative links between implementing the science & recovery

Science Implementation Phase	Example of Recovery
'Stage 1' Vaccine & Some Medicines	Shopping, private healthcare & some sport
'Stage 2' Vaccine & Multiple Medicines	Tourism, travel, dining , entertainment & full sport
'Stage 3' Vaccine & Multiple Medicines	Elderly spending & childcare

Q&A

Appendix A – Vaccines to Watch

Vaccines to Watch - #1 Johnson & Johnson : [Unnamed]

- Vaccine Type : Subunit vaccine (no adjuvant)
- J&J is the world's biggest pharma company
- Started quickly & starting Phase I in September
  - Early start has offset subunit vaccines' development delays
- Phase I results in December 2020
- J&J and US govt. spending $1bn+ to fund development
  - Building manufacturing capacity during 2020
- Crucially, J&J will use semi-proven 'next gen.' sub-unit manufacturing
  - Claim should allow c.1 billion doses per year to be dosed from Q1 21 onwards
- *This is a very strong candidate to be an initial vaccine for a 'Stage 1' roll-out and also to play a key role in 'Stage 2'*

Vaccines to Watch - #2 Sanofi & GSK : [Unnamed]

- Vaccine Type : Subunit vaccine (with the same adjuvant as Shingrix)
- GSK & Sanofi are world's first & fourth largest vaccine players
- Sanofi are the lead developer & have licensed GSK's market-leading adjuvant
  - This adjuvant was also pivotal to the approval of the world's first malaria vaccine
- Sanofi are using next-gen. subunit manufacturing
  - Already proven in an influenza vaccine for the elderly
  - Claim can manufacture up to 1 billion doses a year
- Phase I trials due to start in Q4 20
- Claim regulatory approval could come as early as H2 21
- *This is a strong candidate to be the high potency vaccine required for a 'Stage 3' roll-out to older age cohorts*

Vaccines to Watch - #3 Moderna : mRNA-1273

- Vaccine Type : RNA vaccine (no adjuvant)
- Most advanced RNA vaccine in development
- Phase I began in March, Phase II is due to begin in Q2 20 & Phase III in Q4 20
- Mgt. stated ‘Stage 1’ rollout could start in Q4 20 (for health workers)
- US govt. spending $0.5bn to fund development
  - Mgt. stated could make ‘tens of millions’ doses per month in 2021
  - Mgt. emphasised hiring skilled staff as a key risk
- Initial indications are vaccine (and perhaps RNA class) isn’t very potent
  - Phase I trial testing only 2 dose versions
  - CEO verbally stated a more potent vaccine will be needed for the elderly
- *This is a strong candidate to be the first vaccine ready for a ‘Stage 1’ rollout and could also play a useful role in ‘Stage 2’*

Vaccines to Watch - #4 BioNTech, Pfizer & Fosun: BNT162

- Vaccine Type : RNA vaccine (with no adjuvant)
- A combined Phase I & II trial began in April
- Pfizer (3rd largest vaccine player) agreed to co-finance & co-launch
  - Bought $113m of BioNTech shares & paid an initial $74m milestone
- Fosun agreed to partner for China only
  - Bought $50m of BioNTech shares
- Deal terms very high for an early-stage medicine
- Will manufacture 'hundreds of millions' of doses per year
- Also developing 3 other vaccines using variations of RNA technology
- *The partnering deals are striking and Pfizer also brings manufacturing heft. This vaccine could play an important role in 'Stage 2'.*

Vaccines to Watch - #5 Cansino Biologics : Ad5-nCoV

- Vaccine Type : DNA vaccine (with no adjuvant)
- World's most advanced Covid-19 vaccine
  - Finished its 3 dose level Chinese Phase I trial on 9 April
- BUT the 'high' dose failed in Phase I due to side effects
  - Clear-cut safety failure is rare in vaccine trials
- Has now started Phase II with remaining 'low' and 'medium' doses but…
  - Normally would redo Phase I to understand side effect issues
  - Remaining doses less likely to produce a potent vaccine
- Media reports suggest side effects were also seen with 'medium' dose
  - Side effects may become unacceptable as frailer lives are tested
  - Developed countries now unlikely to approve without full Phase III
- *This example was picked to highlight the risks & attrition rates involved here*

Appendix B – Population Immunity Scenario Assumptions

Variable	Assumption
'Stage 2' Vaccine Effectiveness	Ages 0 – 2 = 0% (i.e. vaccine not effective) Ages 2 – 50 = 75% Ages 50+ = Same as Zostavax
'Stage 3' Vaccine Usage	Ages 60+
'Stage 3' Vaccine Effectiveness	Same as Shingrix
Duration of Vaccine Effectiveness	>=5 years
Population Source	United Nations 2019 Projection – Medium Variant – Year = 2025
Population Take-Up	'Stage 2' 1 dose vaccine = 95% 'Stage 3' 2 dose vaccine = 90%
Children Scenarios	0%, 50% & 100% scale factors applied to ages 0 - 17
Herd Immunity Threshold	67% - 75% (i.e. R_0 = range of 3.0 – 4.0)
Population Already Immune (Prior Infection)	10%