Regulatory importance of generalizability

Florian Klinglmueller

Austrian Medicines and Medical Devices Agency/Biologics, Preclinical and Statistics Assessment

The contents of this presentation are my personal opinion. My remarks do not necessarily reflect the official view of AGES, BASG, EMA, or any associated working party or committee.

All examples rely on data from publicly available sources (EPAR, SmPC). They are presented for illustration purposes and should not be misunderstood as criticism of the product or associated regulatory decisions.

Terminology

What are we talking about

- **Internal validity:** "the validity of inferences about whether observed covariation … reflects a causal relationship" (Shadish et al. 2002)
- **External validity:** "the validity of inferences about whether the cause-effect relationship holds over variation in persons, settings, treatment variables, and measurement variables." (Shadish et al. 2002)
- Randomized controlled trial provide internal validity, but may lack external validity
- **Target validity:** validity of inferences about whether the cause-effect relationship holds for a specific target population (Westreich et al. 2018)
  - Resolves confusion about concepts like transportability, prediction, extrapolation (or any other terms that might be used)

Regulatory importance of generalizability

Do we need to be concerned about generalizability

- "Even when there is no theory, or very weak theory, an RCT, by demonstrating causality in some population can be thought of as proof of concept, **that the treatment is capable of working somewhere**" (Deaton and Cartwright 2018)
- If that is enough to allow a treatment to be marketed, we can stop here
- Unfortunately it is not as easy

COVID-19 Vaccine Valneva

Main immunogenicity study to support authorization

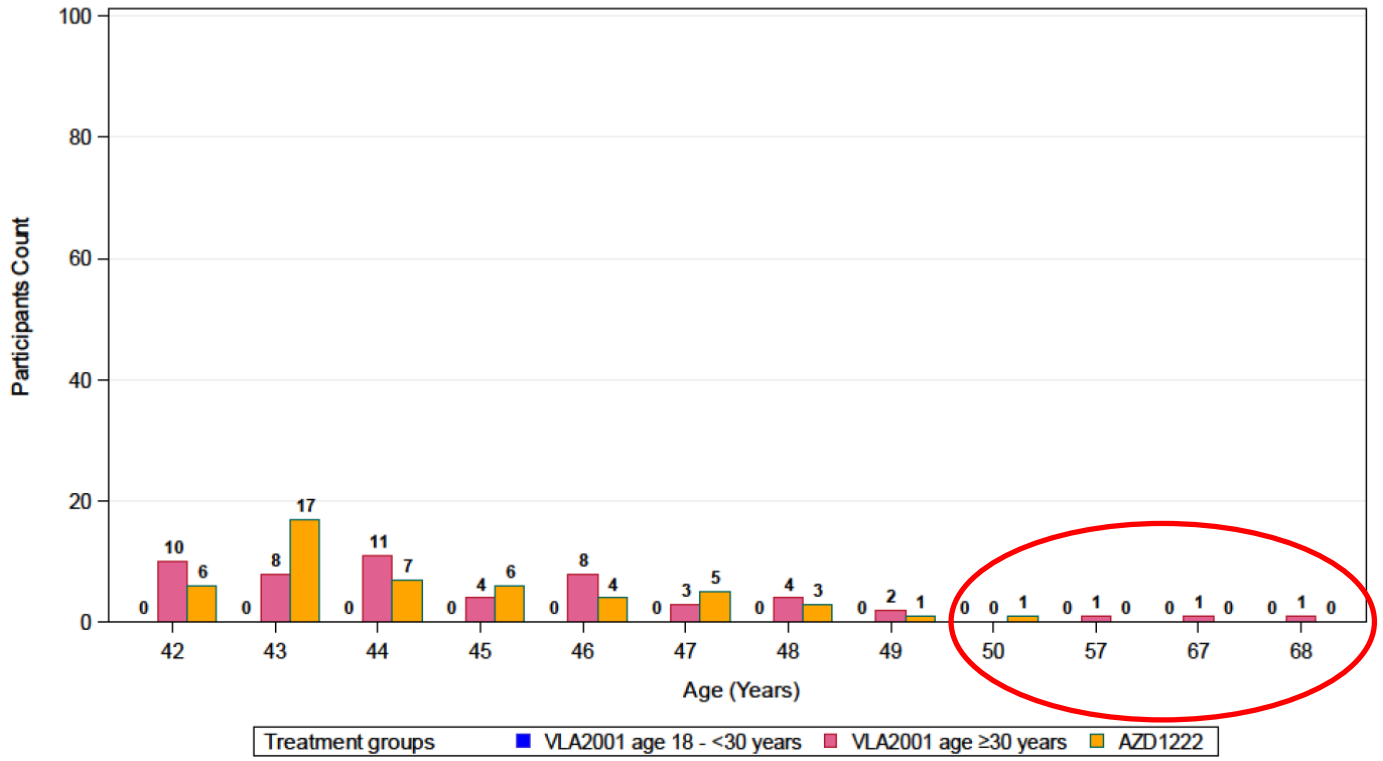
- Inactivated, adjuvanted vaccine for protection against coronavirus disease 2019 (COVID-19).
- **Main Study:** A Randomized, Observer-blind, Controlled, Superiority Study to Compare the Immunogenicity Against COVID-19, of VLA2001 Vaccine to AZD1222 Vaccine, in Adults (VLA2001-301) – conducted in the UK
- **Objective:** Demonstrate superior immunogenicity against COVID-19 compared to AZD1222
- Main age-related inclusion criterion:
  - Participants of either gender aged 18 years and older at screening
- **Results:** Primary endpoint met in the study population

COVID-19 Vaccine Valneva

Study population

- Prior to start of recruitment AZD1222 was contraindicated in the UK for subjects <30yoa, the corresponding cohort was non-randomized
- Apparent difficulties to recruit subjects >55yoa
- In fact very few subjects >50yoa with immunogenicity data

Figure 7: Histogram of age distribution VLA2001-301 (IMM Population, 2 of 2)



Tables and Figures taken from COVID-19 Vaccine Valneva EPAR:
https://www.ema.europa.eu/documents/assessment-report/covid-19-vaccine-inactivated-adjuvanted-valneva-epar-public-assessment-report_en.pdf

COVID-19 Vaccine Valneva

Regulatory decision

- "Based on data comparing the immune response triggered by COVID-19 Vaccine (inactivated, adjuvanted) Valneva with that induced by an authorised COVID-19 vaccine, EMA concluded that COVID-19 Vaccine (inactivated, adjuvanted) **Valneva is expected to be at least as effective as the comparator at protecting against the disease in people aged between 18 and 50 years.**"
- "Additional data from this study also showed that the vaccine is **as effective at triggering the production of antibodies in people aged between 18 and 29 as it is in people aged 30 years and older.**"
- "Based on the data provided, **it was not possible, however, to draw any conclusion on the vaccine's immunogenicity in people above 50 years of age**; therefore, the vaccine is currently recommended only for use in people between 18 and 50 years of age."

Quotes taken from: CHMP summary of positive opinion for COVID-19 Vaccine Valneva
https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-covid-19-vaccine-inactivated-adjuvanted-valneva_en.pdf

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- "Even when there is no theory, or very weak theory, an RCT, by demonstrating causality in some population can be thought of as proof of concept, **that the treatment is capable of working somewhere**" (Deaton and Cartwright 2018)
- If that is enough to allow a treatment to be marketed, we can stop here
- Unfortunately it is not as easy
- For approval need to conclude that the treatment is efficacious (and safe) in the target population – as defined by the indication
- Drug approval requires some assessment of target validity with respect to the target population
- The target population will always differ from the trial population (at least in time)

Generalisation

What does the Bible (ICH E9) say

The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

Firm evidence in support of claims requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. The confirmatory trials should therefore be sufficient to answer each key clinical question relevant to the efficacy or safety claim clearly and definitively. **In addition, it is important that the basis for generalisation (see Glossary) to the intended patient population is understood and explained**; this may also influence the number and type (e.g. specialist or general practitioner) of centres and/or trials needed. The results of the confirmatory trial(s) should be robust. In some circumstances the weight of evidence from a single confirmatory trial may be sufficient.

Further guidance

Relate mostly to (planned) extrapolation

- Reflection paper on Extrapolation of efficacy and safety in paediatric medicine development (EMA/189724/2018)
- ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population (EMA/CPMP/ICH/2711/1999)
- ICH guideline E17 on general principles for planning and design of multi-regional clinical trials (EMA/CHMP/ICH/453276/2016 Rev.1)
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)

Regulatory importance of generalizability

Other aspects where generalizability is of importance

- Information to patients and subscribers on what we know about how the treatment can be expected to work in their context (which may be more specific than the target population)
  - Requires careful and transparent communication of results (e.g. EPAR, SmPC)
- Information to payers and healthcare systems on how to (cost) effectively use the treatment
  - The latter is typically not in the remit of drug approval
  - It is questionable whether trials implemented under the assumption that the treatment might not work are the best place to decide how to best use it
  - Confirmatory trials may not be the most efficient tools to answer corresponding questions (e.g. relative efficacy)

Regulatory Options

What can we do when faced with issues of generalizability

- Request for additional information
  - Request additional analyses (e.g. comparison of immunogenicity in the experimental arms between subjects <30yoa and subjects >30yoa)
  - Meta-analyses (e.g. across *underpowered* trials)
  - Modelling exercises
- Request (or prescribe) additional trials
  - Certain indications require trials in special populations
  - Pre-, Post-marketing authorization

Decisions:

1. Accept generalization
2. Change the target population (e.g. restriction of indication)
3. Deny authorization

Causal inference

Promising tool or over-ambitious hype

- Recent treatment of generalization in causal inference literature e.g.: Pearl and Barenboim (2013), Dahabreh et al. (2020)
- Especially Pearl and Barenboim (2013) stress that questions of external validity rely on causal assumptions, which are not statistical
- Provide conditions under which inferences can be extrapolated to external populations
- Provide methods to transfer results from randomized trials to other populations (unbiased estimation of effect in target population)
- Rely on strong (and likely implausible) assumptions (exchangeability, positivity)
- Require correct specification of either the outcome model or (trial) selection process

Conclusions

- Regulatory decisions always require an assessment of generalizability
- Issues of generalizability are routinely considered in regulatory decision making
- Assessment of potential differences between ‘study population’ and ‘target population’ and whether they could negate a positive benefit risk balance (inferred from trials) is not a primarily statistical problem
- Studies may provide some evidence on ‘effect modifiers’ but this is often based on ‘improper analyses’ and uncertainty is large
- Complete external validity is not possible (the target will change)
- Generalizability is important for efficacy and safety (one may not imply the other)
- Assessment is sometimes ‘informal’

Discussion

Open questions

- To what degree can we rely on an internally valid demonstration in an ‘ideal world’ as afforded by RCT
- Can tools from causal inference/modelling help to make inferences about generalizability more systematic. E.g.:
  - improve transparency in assumptions,
  - identify most relevant threats to generalizability,
  - derive limiting scenarios that would tip B/R,
  - provide guidance how evidence gaps can be closed.
- To what degree can we defer issues of external validity to post-authorization measures and clinical practice (payers, HTA, clinicians and patients)

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DI Dr. Florian Klinglmueller
Senior Expert - Biostatistics

AGES – Austrian Agency for Health & Food Safety

Traisengasse 5
1200 Wien

florian.klinglmueller@ages.at
www.ages.at