Automated SARS-CoV-2 mutation screening

Fabian Amman

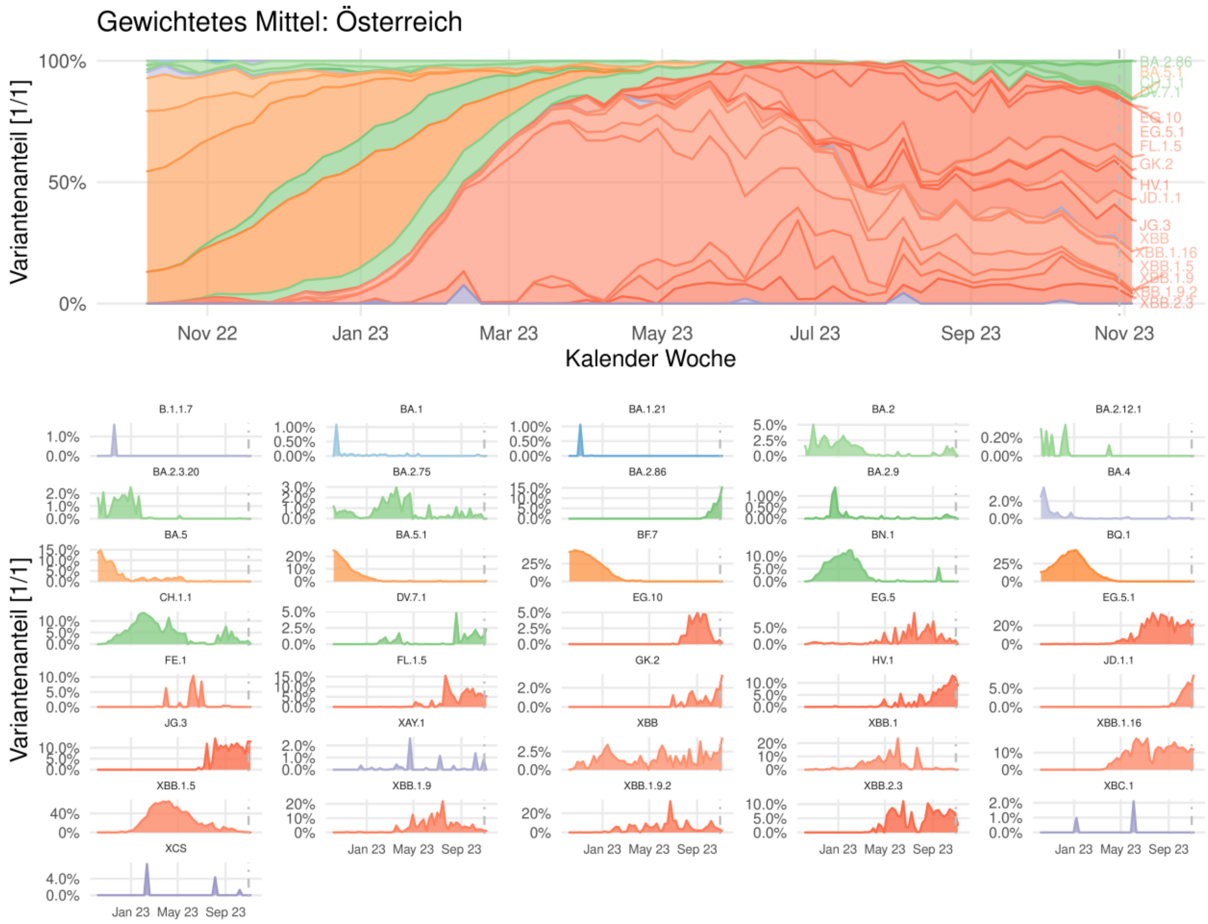
Institute for Hygiene and Applied Immunology
Center for Pathophysiology, Infectiology and Immunology
Medical University of Vienna

SC2 variant surveillance

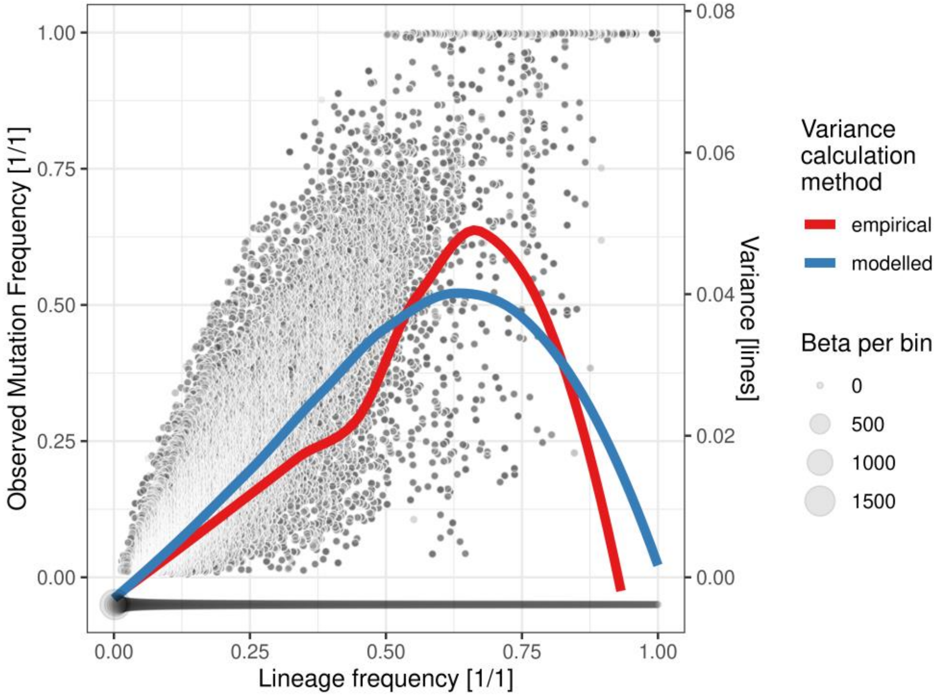
- Variant surveillance can inform …
  - … imminent variant driven waves, as seen with Alpha, Omicron
  - … vaccine development/selection
- Several tools can detect/quantify prior described variants in WW data, e.g., Freyja, LolliPop, Vaquero
- All these tools depends on information gained from comprehensive case-based variant surveillance
  - Prioritization of variants to screen for
  - Characteristic mutations of these variants

- **<u>Problem</u>: case-based variant surveillance becomes more and patchy, in time and space**
- **<u>Challenge</u>: develop an easy-to-use approach to detect emerging variants/mutations of concern with minimized external information dependencies**

Austrian National WW Monitoring; collaboration with Med Uni Innsbruck;
48+ wwtp; weekly sampling; Data from last 12 months; analyzed by Vaquero



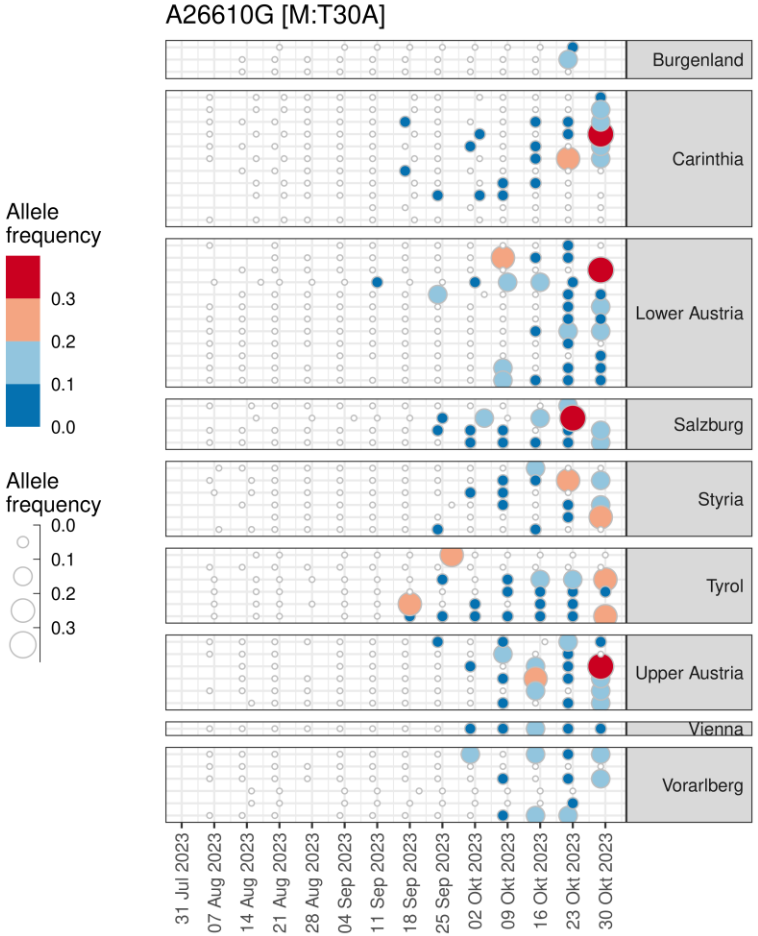
Characteristic mutation quantification



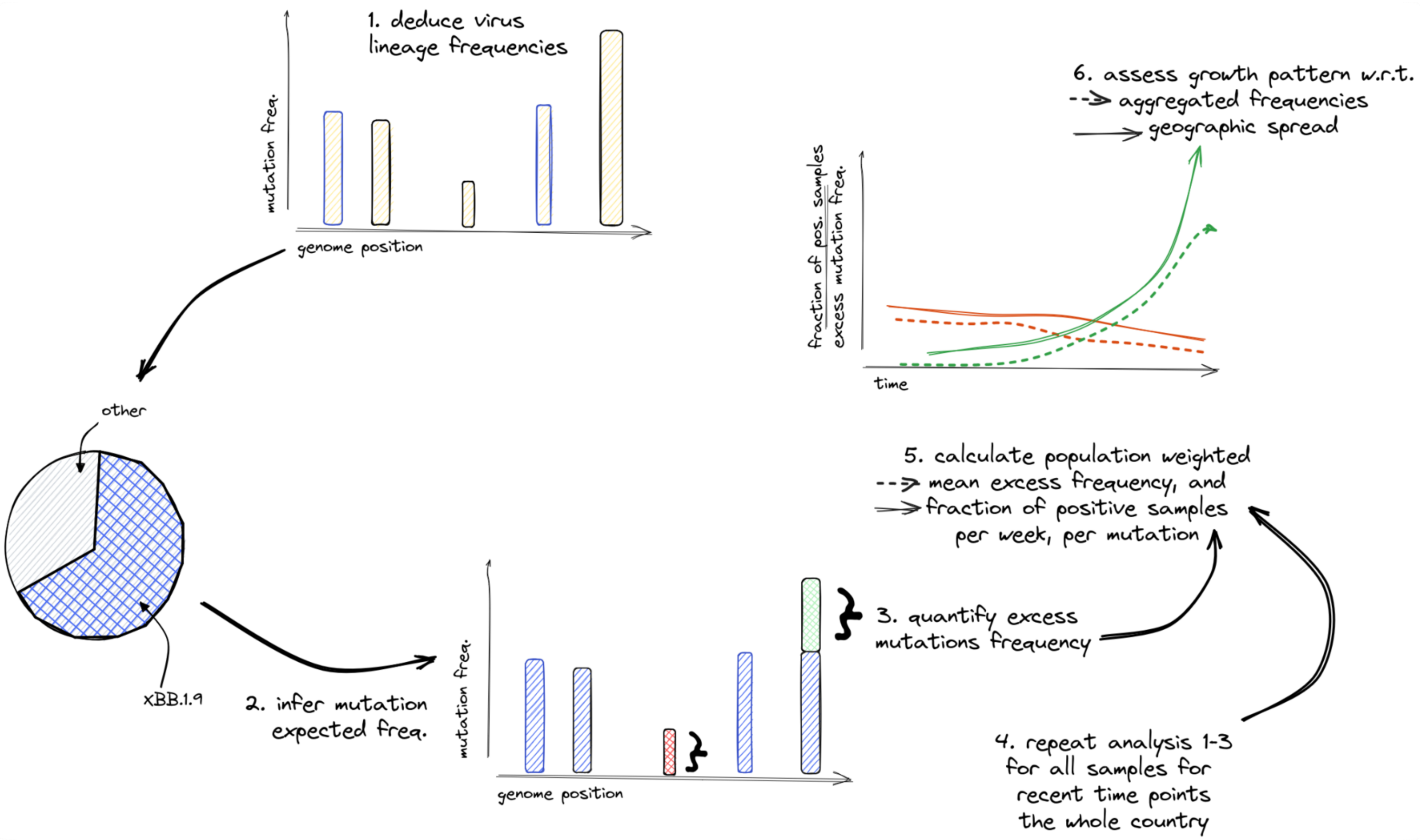
- Observed mutation frequency are a function of host lineage frequency
- Variance exhibit a typical arch-shape, with small variance close to zero and one.
- Observed variance can be decently modelled by a beta distribution, with parameter α and β, so that E[X] = f(α, β) and Var[X] = f(α, β)
- α was estimated to be 3.03

Characteristic mutation spread

- Exemplified by spread of mutation M:T30A, a unique mutation of BA.2.86
- Provided temporal resolution depicts initial intermittent presents in single wwtp
  - Technical artefact close at the LOD?
- No coherent geographic distribution
- Adding geographic breadth smooths patterns
  - Fraction of positive samples per week
  - Population weighted mean mutation frequencies across all samples of same week
- Might prevent detection of sub-geographic spreading variants
  - Are those relevant?



Vaquera: Unexplained growing variants


1. deduce virus lineage frequencies

2. infer mutation expected freq.

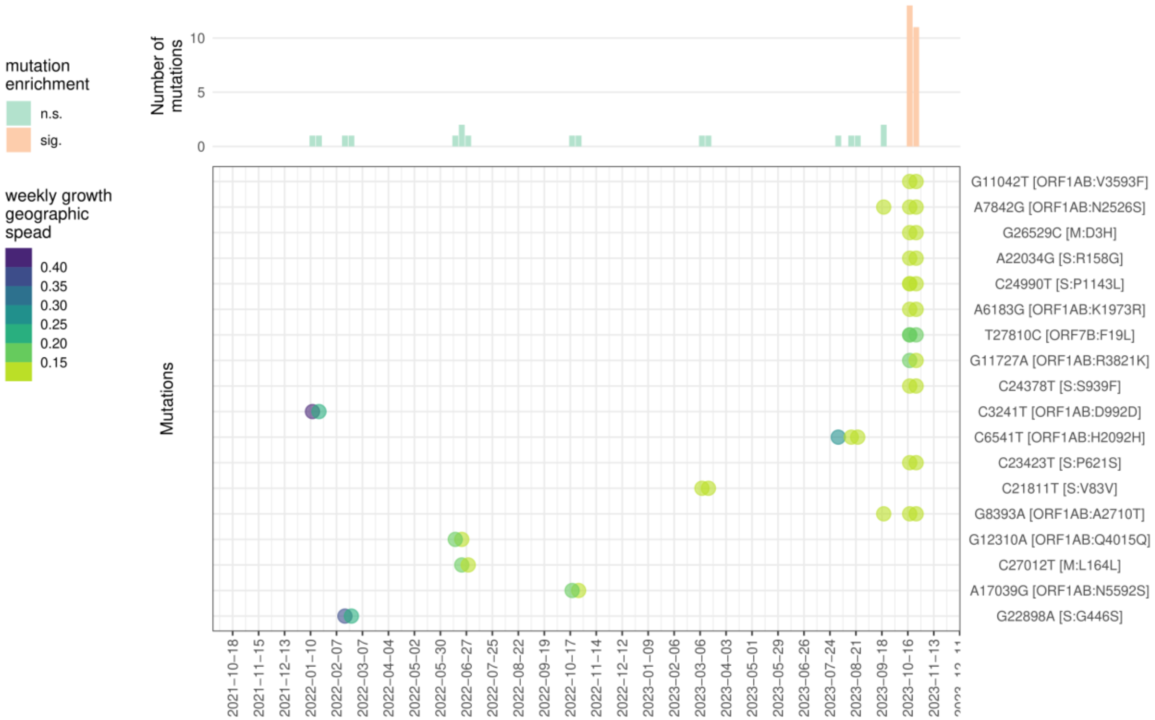
3. quantify excess mutations frequency

4. repeat analysis 1-3 for all samples for recent time points the whole country

5. calculate population weighted
--> mean excess frequency, and
→ fraction of positive samples
per week, per mutation

6. assess growth pattern w.r.t.
--> aggregated frequencies
→ geographic spread

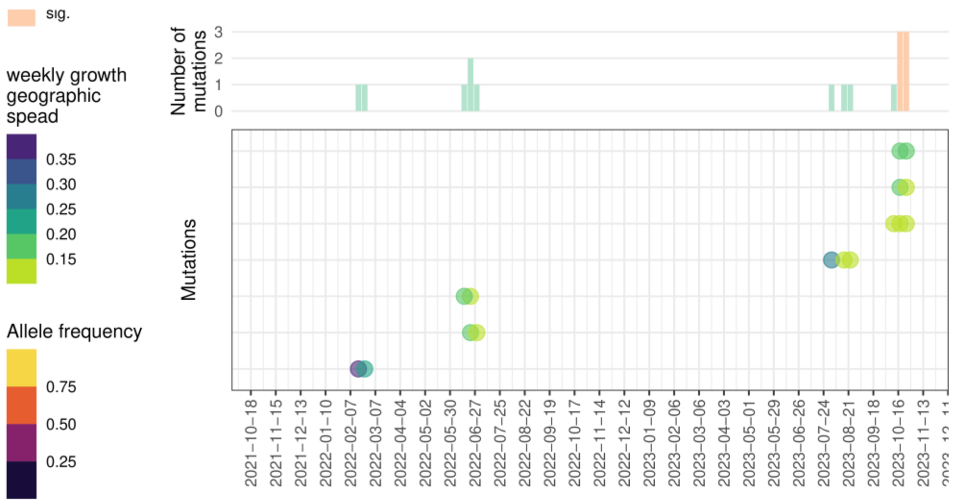
Gedankenexperiment: What if BA.2.86 emerged in Austria?

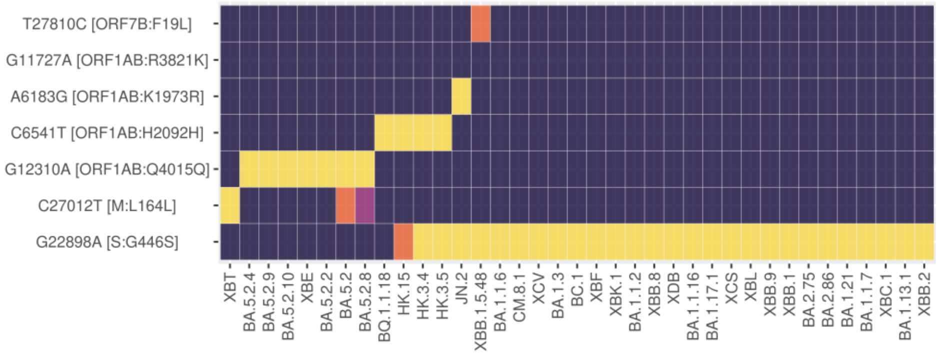


- Current analysis of Austrian National Monitoring data, with most current marker mutation definition based on the MSA provided by GISAID as of Oct 30, 2023 (most recent one)
- Markers for BA.2.86 were deliberately omitted

- First BA.2.86 detection: In the world (GISAID): 2023-07-24; Designation (by PANGO): 2023-08-17; In Austria (WW): 2023-09-11; In Austria (GISAID): 2023-10-04
- Without prior knowledge of BA.2.86, Vaquera would have raised a clear warning signal 2023-10-18

Current analysis results





- Analysis of current Austrian National WW Monitoring data, with most current marker mutation definition, based on the MSA provided by GISAID as of Oct 30, 2023 (most recent one)

- Three mutations (A6183G & G11727A & T27810C) show excess growth, all of which are associated with JN.1
- Current pandemic progression outpaces our data retrieval

Summary: Vaquera

Vaquera Functionality

- Minimal hands on efforts to contextualize hundreds of mutations per sample
- Early warning signal for new, unexplained, growing mutations
- Independent quality assurance for established variant detection / quantification pipelines
- Parametrization allows to fine tune sensitivity / specificity trade off

Data Requirements

- Whole genome sequencing data with prior variant calling
- Surveillance campaign with at least medium sampling density (space and time)
- Compatible with all current sequencing schemes

Code Availability

- Soon on GitHub (*github.com/fabou-uobaf/VaQuERo*)
- Happy to assist, adapt to individual need, etc. Please reach out to ***famman@cemm.at***

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