Integrating virological data in vaccine effectiveness studies

Proposal to IMOVE

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When is it valuable to estimate vaccine effectiveness against a specific genetic group?

- Clade of interest has a low proportion of cases but there is a suspicion of low VE (e.g.: newly circulating clade at the end of the season)
- Several clades are circulating (VE against clade differs to the VE against influenza subtype/lineage)
- Vaccine effectiveness is low

Sample size for 3 scenarios

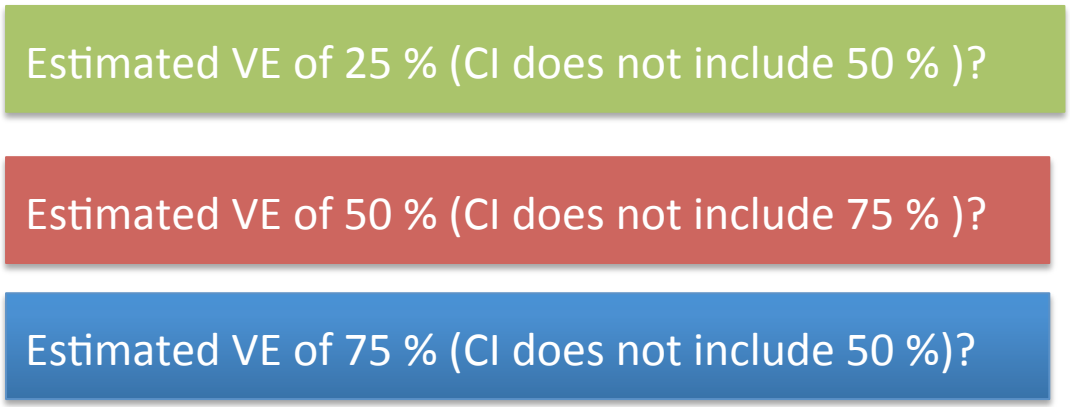


Figure 1.

Sample size (low VE)

Table 1. Conditions for sample size calculation

Proportion of positives for influenza (**P+**)	0.20
Vaccine coverage in negative controls (**P2**)	0.11
Vaccine effectiveness point estimate (VE = **1-OR**)	0.25
Precision of VE (**d** – 95 % CI lower limit = VE - d)	0.35

IMOVE 2014/15 (updated week 9)

Table 2. Estimated sample size

	Cases (clade)	Controls		95 % CI	
				Lower	**Upper**
Vaccinated	34	178			
Non vaccinated	370	1.439	OR= 0.75	0.51	1.10
Total	**404**	1.617	VE= 0.25	-0.10	0.49

Sample size (medium-low VE)

Table 3. Conditions for sample size calculation

Proportion of positives for influenza (**P+**)	0.20
Vaccine coverage in negative controls (**P2**)	0.11
Vaccine effectiveness point estimate(VE=**1-OR**)	0.50
Precision of VE (**d** - 95%CI lower limit= VE - d)	0.35

Table 4. Estimated sample size

	Cases (clade)	Controls		95 % CI	
				Lower	Upper
Vaccinated	17	125			
Non vaccinated	267	1.010	OR= 0.5	0.29	0.85
Total	**284**	1.135	VE= 0.5	0.15	0.71

Sample size (medium-high VE)

Table 5. Conditions for sample size calculation

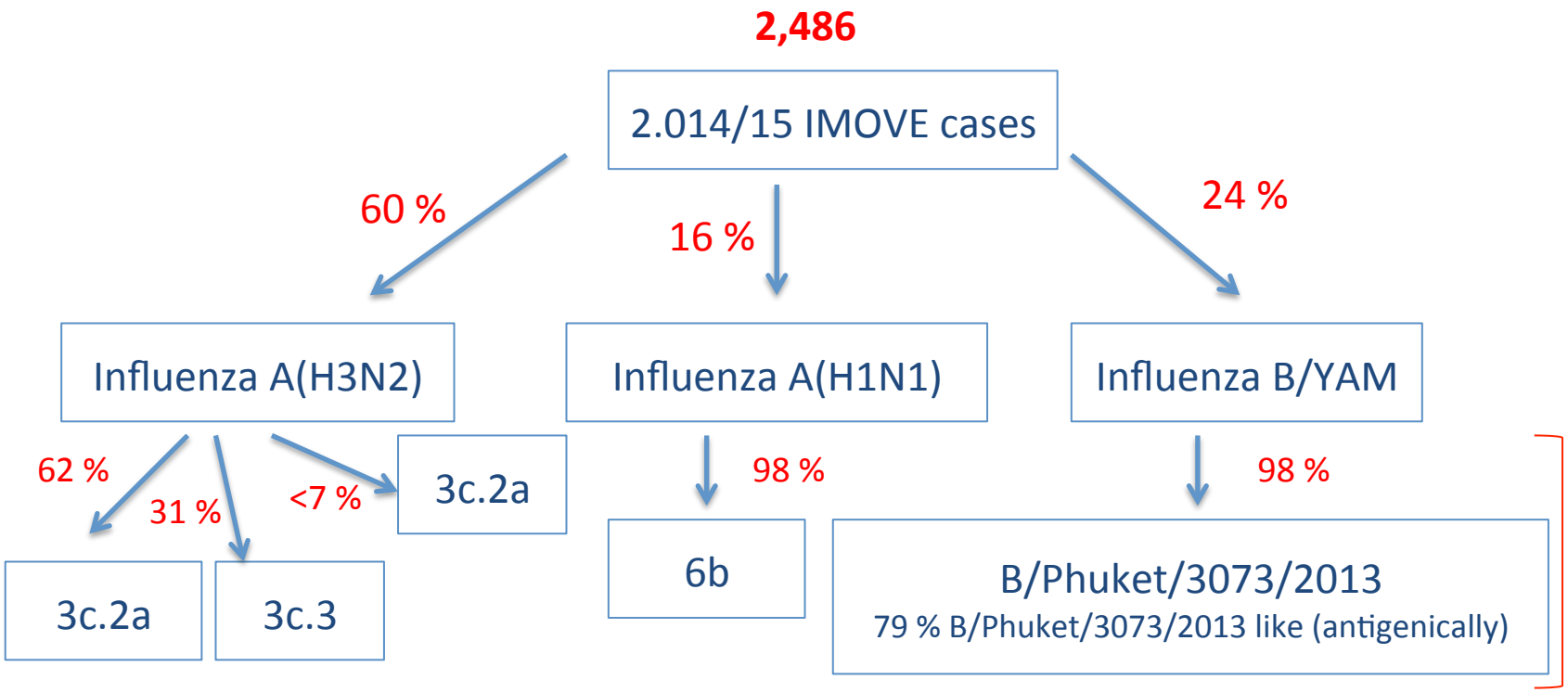
Proportion of positives for influenza (**P+**)	0.20
Vaccine coverage in negative controls (**P2**)	0.11
Vaccine effectiveness point estimate (VE=**1-OR**)	0.75
Precision of VE (**d** – 95 % CI lower limit = VE - d)	0.24

Table 6. Estimated sample size

	Cases clade	Controls		95 % CI	
Vaccinated	9	138		**Lower**	**Upper**
Non vaccinated	304	1.116	OR= 0.25	0.13	0.49
Total	**313**	1.254	VE= 0.75	0.51	0.87

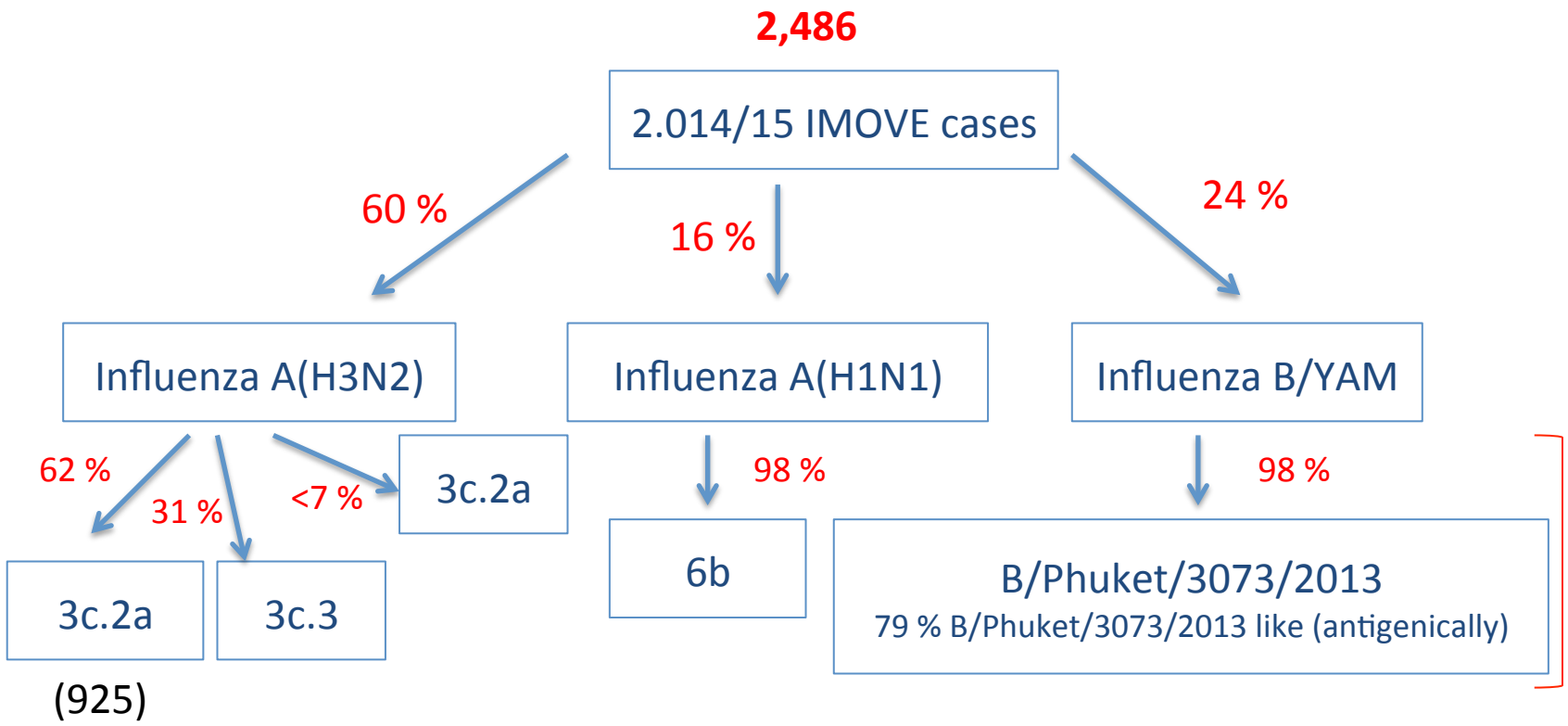
On which situations is it possible to estimate vaccine effectiveness against a specific genetic group?

(for a similar 2014/15 IMOVE number of cases)



number of estimated 3c.2a cases in 2014/2015 IMOVE = 0.62 x 0.60 x 2,486 = **925**

➔ **it is possible to get the number of cases needed to estimate vaccine effectiveness against A(H3N2) 3c.2a**



404 3c.2a aimed cases

404:0.62 = 652 A(H3N2) cases to be selected for virus characterization

652 : (0.6 x 2,486) x 100 = 44 % (sampling fraction)

Sampling fraction (low VE)

2014/15 IMOVE cases = 2,486 (60 % A(H3N2))
3c.2a = 62 % (Flunews Europe, week 20/2015)
Adjusted VE = 22.8 %
Aimed to get 404 cases falling in 3c.2a group ➔ genetic characterization of 44 % of A(H3N2) cases enrolled

Percentage of cases of the influenza sub-type/lineage falling in the clade of interest

Percentage of influenza cases positive for the sub-type/B lineage studied	10	20	30	40	50	62	70	80	90
10	16.16	8.08	5.39	4.04	3.23	2.69	2.31	2.02	1.80
20	8.08	4.04	2.69	2.02	1.62	1.35	1.15	1.01	0.90
30	5.39	2.69	1.80	1.35	1.08	0.90	0.77	0.67	0.60
40	4.04	2.02	1.35	1.01	0.81	0.67	0.58	0.51	0.45
50	3.23	1.62	1.08	0.81	0.65	0.54	0.46	0.40	0.36
60	2.69	1.35	0.90	0.67	0.54	**0.44**	0.38	0.34	0.30
70	2.31	1.15	0.77	0.58	0.46	0.38	0.33	0.29	0.26
80	2.02	1.01	0.67	0.51	0.40	0.34	0.29	0.25	0.22
90	1.80	0.90	0.60	0.45	0.36	0.30	0.26	0.22	0.20

A(H3N2) cases

Table 7. A(H3N2) cases to be selected by country for genetic characterization (2014/2015 IMOVE season – preliminary results)

	A(H3N2) cases (IMOVE 2014/15) N	A(H3N2) cases gen. characterized* N	A(H3N2) cases to be selected for gen. caract. N
Pooled	**1,495**	**108**	**652**
Germany	633	**31**	**276**
Hungary	163	**2**	**71**
Ireland	94	**17**	**41**
Italy	143		**62**
Poland	0		**0**
Portugal	42	**19**	**18**
Romania	70	**7**	**31**
Spain	350	**32**	**153**

*available data on July 08, 2015

B cases

Table 8. B influenza cases to be selected by country for antigenetic characterization (2014/2015 IMOVE season – preliminary results)

	B cases N	B cases genetic characterized* N	B cases to be selected for gen. caract. N
Pooled	**597**	79	**359**
Germany	115	31	**69**
Hungary	11	-	**7**
Ireland	18	7	**11**
Italy	61	-	**37**
Poland	18	-	**11**
Portugal	98	11	**59**
Romania	30	5	**18**
Spain	246	25	**48**

*available data on July 08, 2015

Case Selection

Virological Surveillance

Aims

- Characterization of the circulating influenza viruses:
  - Identify emerging strains with pandemic potential
  - Detect antiviral susceptibility
- To contribute to the WHO Vaccine Strain Selection Committee for vaccine composition of next season
  - Describe drift away from current vaccine strain
  - Identify future vaccine strains

Selection of specimens

- Period of sampling
  - before, during and after the epidemic; interepidemic period
- Geographical representativity
- Sometimes try to cover all age ranges
- Selection specimens from:
  - Every positive specimen from minor circulation
  - Outbreaks
  - Severe patients/ Deaths by influenza
  - Suspected antiviral resistence
  - Vaccine failures
- In the case of antigenic characterization (successful virus isolation: high viral load)

Courtesy of Amparo Larrauri

Vaccine effectiveness studies

Aims

- Evaluation of VE of the influenza vaccine: observational studies
  - Specific outcome: laboratory confirmed influenza
  - Control group should represent the source population of influenza cases
  - Sample testing behavior should not be influenced by patient vaccination status
  - Influenza detection decreases with time since onset, the potential misclassification of cases as controls should be limited
  - Collect information of possible confounding factors

Test negative design

Recruitment of patients

- Cases and controls are selected independently of their case control status
- The study design adjusts for propensity to seek care
- Systematic sampling

Analysis

- Restricted to ILI patients tested within less the eight/four days of onset of symptom
- Adjust for confounders

Courtesy of Amparo Larrauri

Selection bias?

Table 9. 2014/15 EVA cases by genetic characterization and vaccination status (Portugal)

	Genetic characterization (-)	Genetic characterization (+)	Total
Season vaccine (-)	114 (91.2 %)	22 (73.3 %)	136 (87.7 %)
Season vaccine (+)	11 (8.8 %)	8 (26.7 %)	19 (12.3 %)
Total	**125 (100.0 %)**	**30 (100.0 %)**	**155 (100.0 %)**

Note: Available data for 30 out of 32 genetic characterized cases

Table 10. 2014/15 cycEVA cases by genetic characterization and vaccination status (Spain)

	Genetic characterization (-)	Genetic characterization (+)	Total
Season vaccine (-)	699 (90.3 %)	55 (96.5 %)	774 (93.1 %)
Season vaccine (+)	75 (9.7 %)	2 (3.5 %)	77 (9.2 %)
Total	**774 (100.0 %)**	**57 (100.0 %)**	**831 (100.0 %)**

Case selection

- Integration of all the surveillance data will not guarantee exclusion of selection bias

- Beside the virological surveillance system, a random sample of cases should be used to genetic characterization.

- Random selected cases matching those already characterized by NIC will be integrated both on surveillance and VE studies

Case selection

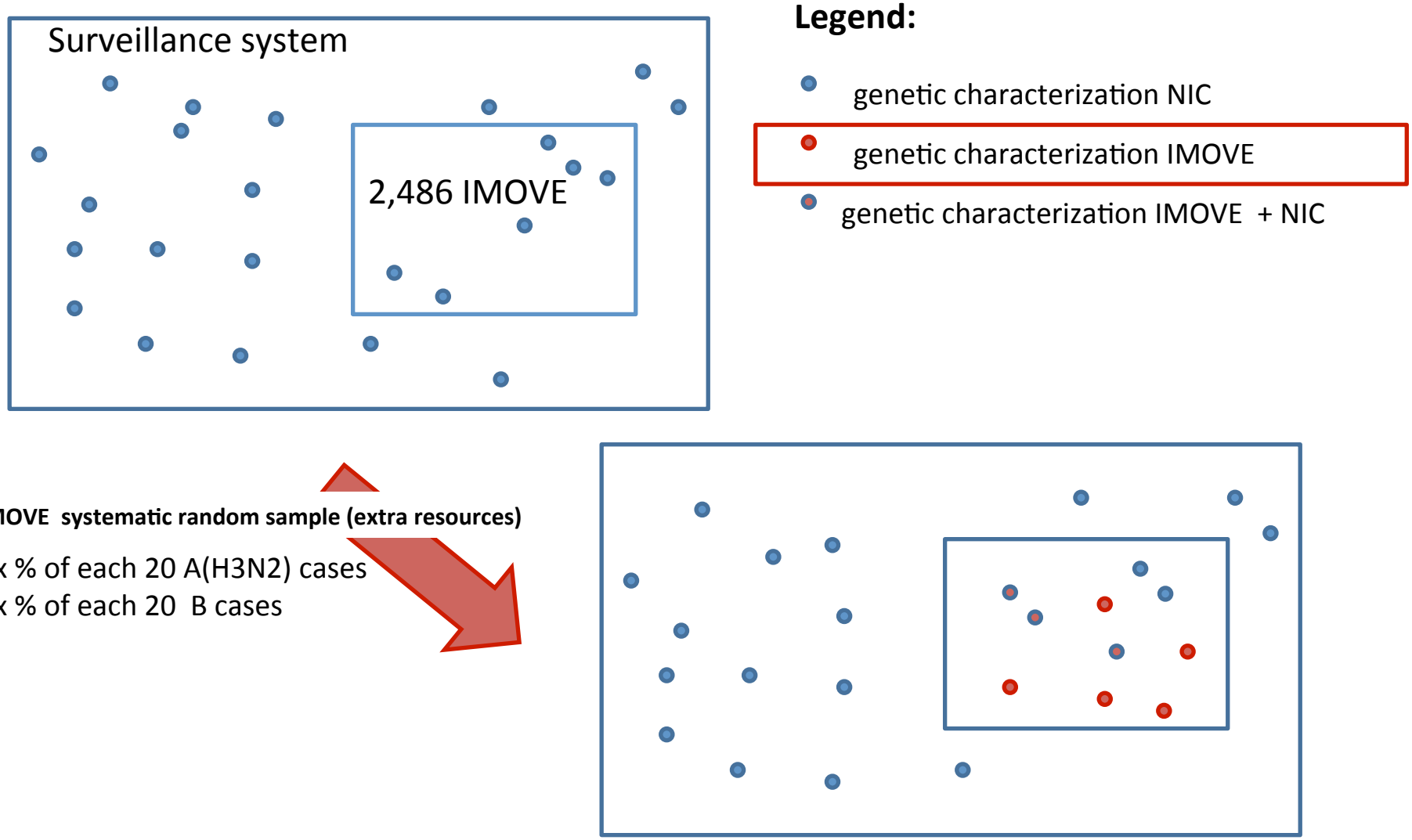


Figure 1. Schematic case selection for genetic characterization in IMOVE

Case study

Table 11. Portuguese data

	Total EVA cases (2014/15)	EVA (randomly selected cases)	EVA gen. charact by NIC	EVA cases randomly selected already gen. charact by NIC	Extra
A(H3)	48	22	19	8	**14**
B/YAM	105	63	11	3	**62**
AH1pdm09	2	0	2	0	**0**

Table 12. Spanish data

	Total cycEVA cases (2014/15)	cycEVA (randomly selected cases)	cycEVA gen. charact by NIC	cycEVA cases randomly selected already gen. charact by NIC	Extra
A(H3)	440	153	35	-	**118-153**
B/YAM	361	48	25	-	**23-48**

Key message

- Even for low VE it would be feasible to estimate VE against a specific genetic group within IMOVE sample if:
  - the proportion of the influenza subtype/lineage is above 50 %
  - the proportion of cases falling in the clade of interest is above 40 %
  - extra resources are available

Future perspectives

- To pilot a systematic randomly selection along the season
  - low sampling fraction
  - Does not interfere with virological surveillance

- Find a case selection scheme that respect virological surveillance and VE studies criteria

Alin Manuel Gherasim, Amparo Larrauri e Francisco Pozo Sanchez

Ana Paula Rodrigues, Ausenda Machado, Baltazar Nunes, Pedro Pechirra, Raquel Guiomar

Thank you!

Extra slides

Sampling fraction (medium-low VE)

2014/15 IMOVE cases = 2.486 (24 % B)
All fell in clade 3; 79 % B/Phuket/3073/2013 like
Ajusted VE = 55.3 %
284 cases falling in B/Phuket/3073/2013 like➔ characterization of 60 % of B cases enrolled

Percentage of cases of the influenza sub-type/lineage falling in the clade of interest

Percentage of influenza cases positive for the sub-type/B lineage studied	10	20	30	40	50	60	70	79	90
10	11.36	5.68	3.79	2.84	2.27	1.89	1.62	1.42	1.26
24	5.68	2.84	1.89	1.42	1.14	0.95	0.81	**0.60**	0.63
30	3.79	1.89	1.26	0.95	0.76	0.63	0.54	0.47	0.42
40	2.84	1.42	0.95	0.71	0.57	0.47	0.41	0.36	0.32
50	2.27	1.14	0.76	0.57	0.45	0.38	0.32	0.28	0.25
60	1.89	0.95	0.63	0.47	0.38	0.32	0.27	0.24	0.21
70	1.62	0.81	0.54	0.41	0.32	0.27	0.23	0.20	0.18
80	1.42	0.71	0.47	0.36	0.28	0.24	0.20	0.18	0.16
90	1.26	0.63	0.42	0.32	0.25	0.21	0.18	0.16	0.14

Sampling fraction (medium-high VE)

Number of cases: 2,486 (2014/2015 IMOVE sample)
VE = 75 % (and higher than 50 %)
Sample size needed: 313

Percentage of cases of the influenza sub-type/lineage falling in the clade of interest

Percentage of influenza cases positive for the sub-type/B lineage studied	10	20	30	40	50	60	70	80	90
10	12.52	6.26	4.17	3.13	2.50	2.09	1.79	1.57	1.39
20	6.26	3.13	2.09	1.57	1.25	1.04	0.89	0.78	0.70
30	4.17	2.09	1.39	1.04	0.83	0.70	0.60	0.52	0.46
40	3.13	1.57	1.04	0.78	0.63	0.52	0.45	0.39	0.35
50	2.50	1.25	0.83	0.63	0.50	0.42	0.36	0.31	0.28
60	2.09	1.04	0.70	0.52	0.42	0.35	0.30	0.26	0.23
70	1.79	0.89	0.60	0.45	0.36	0.30	0.26	0.22	0.20
80	1.57	0.78	0.52	0.39	0.31	0.26	0.22	0.20	0.17
90	1.39	0.70	0.46	0.35	0.28	0.23	0.20	0.17	0.15