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Manuscript title:

Mumps outbreak, Republic of Moldova, 2007-2008

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Running head: Mumps outbreak, Moldova

Abstract

Background: Moldova experienced a nationwide mumps outbreak in 2007-2008. Single-dose monovalent mumps vaccination at 15-18 months was introduced in 1983, replaced by a two-dose MMR schedule at age 1 and 6-7 years in 2002. We investigated the outbreak to quantify its extent, explore the role of primary and secondary vaccine failure, and provide control recommendations.

Methods: We analyzed national mumps surveillance and vaccination coverage data to estimate vaccine effectiveness (VE) using the screening method. A retrospective cohort study in five educational institutions was conducted to determine age-specific attack rates (ARs) and VE. We compared vaccine strain-specific ARs. Isolation and genotyping of mumps virus strains were performed.

Results: Of 31,142 cases reported during October 2007-July 2008, 80% were 15-24 years old. Of cases with information (66%), 92% were vaccinated once, 4% twice. One-dose mumps VE estimates based on surveillance data over 1997-2001 declined from 91% (95%CI 88-92%) in 2 year-olds to 72% (70-74%) in 15-19 year-olds. In the cohort study (n=1,589), VE was -40% (-120 to 20%) for one dose. For two doses it was 62% (-43 to 90%) in 13-15 year-olds. ARs were higher in individuals vaccinated with Urabe strains (43%) than with Leningrad-Zagreb strains (14%, P<0.001). Mumps virus genotype G5 was identified.

Conclusions: Low effectiveness of single-dose mumps vaccination was the main cause of the outbreak. Waning immunity may have contributed to this. The risk of mumps in two-dose vaccinees was low. Other countries in which large population groups have received <2 doses of mumps vaccine may face similar outbreaks.

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Manuscript

Introduction

Since the 1960s, the introduction of mumps vaccination led to a dramatic decrease in mumps incidence (1;2). However, outbreaks of mumps in highly vaccinated populations have since been reported, raising questions about mumps vaccine effectiveness (VE) (2;3). Low VE may be due to primary vaccine failure (PVF, failure to mount an immune response), secondary vaccine failure (SVF, waning of vaccine-induced immunity) and reduced cross-protection against wild-type mumps virus (MuV) infection provided by the vaccine strain (4).

All mumps vaccine strains, except Rubini, yielded efficacy estimates over 95% in the original accreditation randomized controlled clinical trials. However, lower effectiveness estimates were observed in outbreak studies, for example 77% for the Jeryl-Lynn and the Urabe strain (5).

The Republic of Moldova (Moldova) introduced single-dose monovalent mumps vaccination in 1983 for 15-18 month-old children. Vaccine strains used were Leningrad-3 (1983-1990), Leningrad-Zagreb and Urabe-Am9 (both after 1990). Vaccine shortages led to an interruption of the program in 1995-1996. Successful catch-up vaccination for affected birth cohorts was carried out in subsequent years. In 2002, a two-dose combined measles-mumps-rubella vaccination (MMR) schedule for 12 month-olds and 6-7 year-olds was introduced using Jeryl-Lynn, Urabe-Am9, and Leningrad-Zagreb strains. Reported mumps vaccination coverage (VC) among birth cohorts from 1978 onwards exceeded 95%. A large mumps outbreak occurred in 1996-1998 with 28,845 cases reported predominantly in individuals of early school-age (7-14 years). From 1999 through 2004, the annual incidence of reported cases was <100, and as of 2005 even <10 cases per 100,000 (6).

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In October 2007, the monthly number of reported mumps cases increased to 105 compared to a monthly average of 24 from January-September. By the end of January 2008, a total of 6,613 cases had been reported. Surveillance data indicated that a high proportion of cases had been vaccinated against mumps suggesting vaccine failure caused the outbreak. The aim of our investigation was to describe extent and characteristics of the outbreak, to explore the role of PVF and SVF, and to identify the genotype of the circulating mumps virus in order to contribute information regarding cross-protection afforded by the vaccine.

Materials and Methods

Outbreak description

In Moldova, mumps is notifiable to the regional public health authorities when suspected on clinical grounds by health-care staff. Aggregated notification data are reported to the national level monthly and annually categorized into eight age-groups (<1, 1, 2, 3-6, 7-14, 15-19, 20-29, and >29 years). From week 51, 2007, cases were reported weekly in response to the outbreak.

Assessment of vaccine effectiveness and the role of SVF

We estimated the VE by the screening method (7) (see on-line appendix) and by carrying out a cross-sectional study at five educational institutions with high attack rates (AR; ≥10%), a wide age-range of pupils (6-24 years), available vaccination data, and available medical staff to assist with data collection. We used a self-administered questionnaire to collect information on socio-demographic status, risk factors for exposure to mumps, disease history, symptoms, and hospital stay due to mumps. Study participants aged <15 years were asked to complete the questionnaire with their parents. We assumed implicit informed consent when the questionnaire was completed. Information on vaccination status, lot number and disease history for measles,

mumps, and rubella were obtained from the medical record of the sanitary service of the educational institution. The delivery register of the national vaccine store available from 1997 onwards was used to link vaccine strains to lot numbers. We considered April-September as warm and October-March as cold season. We assumed that PVF due to cold chain failure is more likely to occur during the warm season.

Mumps was defined as self-reported unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting ≥2 days or as a mumps diagnosis in the medical record, with a date of onset after September 2007. We excluded individuals without vaccination records and those with a self-reported history of mumps before 2007.

We compared ARs by age, educational institution, vaccine strain and season of vaccination using the Chi-square test. We estimated VE for one and two doses of mumps vaccine compared to zero doses, stratified by age-group, as 1-relative risk. Where group size permitted this, we calculated VE estimates adjusted for other risk factors according to the formula VE=1-odds ratio, whereby the odds ratio was estimated using multivariable logistic regression as outlined in the on-line appendix. Confidence intervals (CI) were calculated using the exact method.

Stata version 10 was used for all analyses (8).

Laboratory investigations

Real-time MuV specific polymerase chain reaction (RT-PCR; (9)) was performed on oral fluid samples from 18 hospitalized patients. RT-PCR positive samples were confirmed by nested PCR and genotype information obtained by analysis of the SH gene as previously described (10).

Results

Outbreak description

Between October 2007 and July 2008, 31,142 mumps cases were reported in all regions of Moldova. The outbreak peaked at the end of March 2008 (week 14) with 2,351 new cases. The monthly incidence increased from an average <1/100,000 in January-September 2007 to 202/100,000 in March 2008 (**Figure A1**).

Cases occurred in all age-groups. Forty percent were in 15-17 year-olds, 80% in 15-24 year-olds; 58% were male. Thirty-six percent of cases were hospitalized, mainly for isolation purposes. No deaths due to mumps were reported. Vaccination status was available for 10,257 (66%) of 15,540 cases notified between week 51/2007 and the start of supplementary immunization activities (SIA) in week 10/2008. Of these, 92% were vaccinated once against mumps, 4% twice.

RT-PCR confirmed mumps in all tested samples. Eight samples were sequenced (Genbank number GQ370467) and all were an identical G5 genotype, similar to G5 sequences found in other parts of Europe.

Cross-sectional study

Three schools in rural areas, one college and one university (both in urban areas) participated to our cross-sectional study. Data were collected between 28 February and 5 March 2008. We received 1,820 completed (93% of distributed) questionnaires. We excluded 231 (13%) individuals from the analyses. The age-range of the remaining study population (n=1,589) was 6-25 years (median 15), 54% were male. Ten percent were unvaccinated, 52% had received one dose and 35% two doses of mumps vaccine.

Of all participants, 294 met the case definition (AR 19%). The highest AR (42%) was in 16 year-olds (**Figure 1**). ARs varied from 9% (university) to 27% (school 2) between study locations (P<0.001). Of the 294 cases, 11% were unvaccinated, 80% had received one dose and 9% two doses of mumps vaccine. ARs did not differ between males (19%) and females (18%, P=0.81).

Of 238 cases with available medical records (81%), parotid swelling was reported in 89%, pancreatitis in 27%, and hearing impairment in 7%. Orchitis was reported in 12% of male cases (63% of these bilateral).

ARs in individuals vaccinated with one dose of monovalent mumps vaccine (n=819, 52%) were lower when the vaccine had been administered in the warm compared to the cold season (25% vs. 33%, P=0.02). In two-dose vaccinees (one dose of monovalent mumps followed by one dose of MMR vaccine, n=560) the ARs did not differ significantly by season of vaccination (P=0.28).

We had information on used vaccine strain for 278/819 participants (34%) vaccinated with one dose of monovalent mumps vaccine between 1997 and 2002. The AR was 43% (30/70, 95%CI 32-55%) in individuals vaccinated with the Urabe strain (between 1998 and 2001) and 14% (29/208, 95%CI 9-19%) in individuals vaccinated with the Leningrad-Zagreb strain (all in 1997).

The adjusted VE for one dose of monovalent mumps vaccine was -40% (95%CI -120 to 20%). There was a trend of a decrease in adjusted VE by age-group. We could not calculate an adjusted VE for two doses of mumps vaccine (one dose of monovalent followed by one dose of MMR) due to low numbers of individuals. The crude VE for two doses was 62% (-43 to 90%) in 13-15 year-olds (**Table 1**).

Results from the risk factor analysis and the historical VE which were estimated using the screening method are presented in the on-line appendix.

Discussion

Between October 2007 and July 2008 Moldova faced a large nationwide mumps outbreak. Most cases were in teenagers and young adults (15-24 years) vaccinated with one dose of mumps vaccine. The adjusted VE for one dose of monovalent mumps vaccine in a study cohort was very low (-40%). There was a decline in VE with increasing age. We found some evidence for a higher AR in individuals vaccinated once with the Urabe strain compared with the Leningrad-Zagreb strain.

Our cohort study was designed with the primary aim to identify reasons for vaccine failure, as the vast majority of cases occurred in vaccinated individuals. It lacked power to estimate the VE with adequate precision. Our estimated VE for one dose of monovalent mumps vaccine was below zero, which is biologically not plausible. Circulation of MuV in Moldova in the past, notably during the 1997/98 outbreak, would have infected unvaccinated individuals at a higher rate leading to an underestimation of the AR in unvaccinated and thus underestimating the VE. Although we excluded individuals with a history of mumps, residual confounding is likely to be present as mumps is often asymptomatic.

Explanations for the low VE estimates include SVF and PVF and reduced cross-protection afforded by vaccine strains against the outbreak strain.

We observed a decrease in mumps VE with age for one dose of mumps vaccine, both in our cross-sectional study and by using the screening method. This would be consistent with SVF. However, residual confounding due to past infection is probably stronger in older age-groups

and limits the conclusions that can be drawn from the observed decline in VE by age-group. A planned serological study of pre-outbreak samples will provide information on age-specific pre-existent immunity and aid interpretation of our VE estimates.

Waning of mumps vaccine-induced immunity has been suggested in other outbreak investigations (11;12). Serological surveys in high-coverage settings with low wild MuV exposure suggest a decrease of anti-MuV antibodies over time. However, to date this has not been shown to be linked to a decrease in protection (13-16). There is also evidence for long persistence of cellular immunity (17). This is supported by other studies where no evidence for waning immunity was found (18;19).

Our analyses regarding PVF were limited to comparing season of vaccine administration and did not include other potential reasons for PVF as only anecdotal information on this was available. We cannot explain the higher AR in individuals vaccinated in the cold season, but our results argue against a cold chain failure.

Reduced cross protection afforded by vaccine strains against the G5 strain might have contributed to the extent of this outbreak. Good cross protection between genotypes has been observed in several outbreaks (20;21) and there is serological and phylogenetic evidence of monotypic immune response to different MuV strains (22). However, lower levels of neutralizing antibody titers against antigenically different MuV strains have been demonstrated (23), and the level of cross protection may depend on absolute antibody levels. Other studies also provided some evidence for mumps vaccine-induced immunity being less effective against heterologous wild virus strains (3;23-25). A population-based serosurvey which will allow assessing the level of protection provided by vaccine-induced antibodies against different wild-type MuV strains is currently being carried out.

The proportion of orchitis in males is comparable to what has been reported elsewhere (5), however, the proportion of cases with pancreatitis is probably an overestimation as the diagnosis was based on elevated serum amylase irrespective of clinical symptoms. The hospitalization rates were much higher than reported for other mumps outbreaks (3), however, the majority was hospitalized for isolation purposes. Considering the peak in infectivity prior to symptom onset in mumps (26) hospitalization is unlikely to contribute to mumps control.

The mumps outbreak with >31,000 cases overwhelmed the Moldovan health system. Our findings, and those elsewhere (27), suggest that countries where large population groups have received less than two doses of mumps vaccination may experience outbreaks, and support WHO's recommendation of introducing a second dose of mumps vaccine in the routine vaccination schedule (28). Countries should assess the need to offer a second dose of mumps vaccine to populations who have received only one dose of mumps vaccine.

Acknowledgments

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Figure 1: Number of cohort study participants and attack rate (AR) by age, Republic of
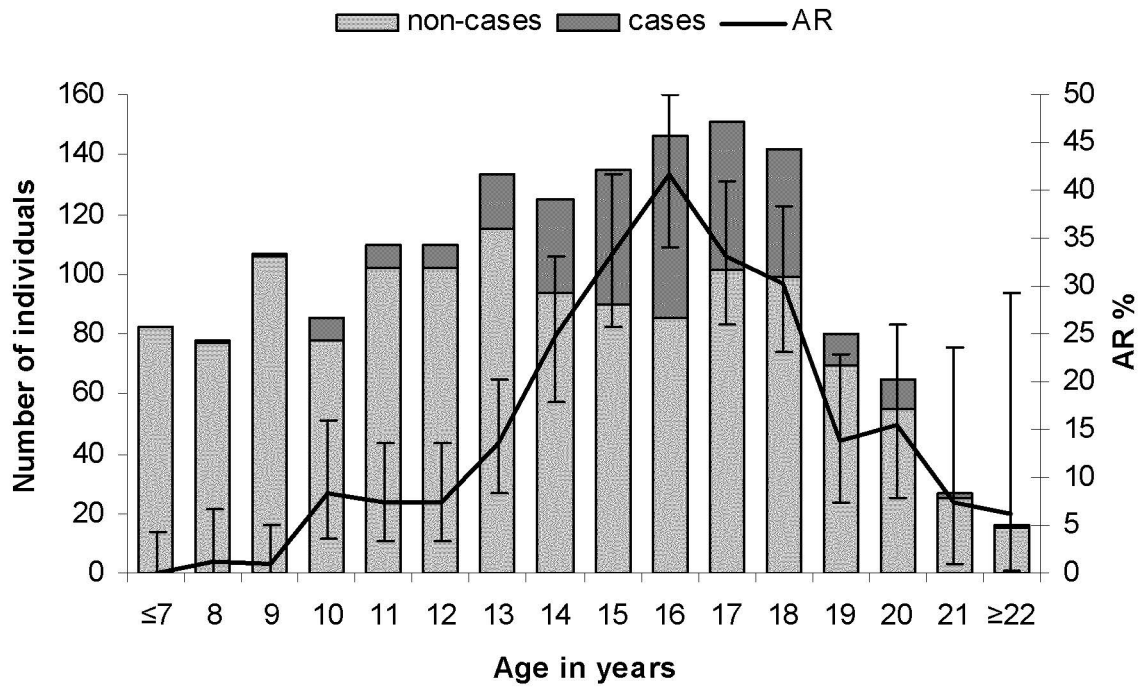
Moldova, March 2008 (n=1,589).

Table 1: Attack rates (ARs) and (adjusted = a) vaccine effectiveness (VE) estimates by age-group for a single dose of monovalent mumps vaccine and the combination of 1 dose of monovalent mumps followed by 1 dose of MMR vaccine derived from the cohort study, Republic of Moldova, March 2008.

Age (years)	0 doses		1 dose (monovalent mumps vaccine)						2 doses (monovalent mumps followed by MMR vaccine)			
	n	AR (%)	n	AR (%)	VE (%)	95%CI (%)	aVE* (%)	95%CI (%)	n	AR (%)	VE (%)	95%CI (%)
6-9 (N=251)	1	0	7	0	-	-	-	-	243	0.4	-	-
10-12 (N=293)	0	-	5	0	-	-	-	-	288	6.6	-	-
13-15 (N=375)	13	30.8	336	24.4	21	-0.8 to 66	30	-140 to 80	26	11.5	62	-43 to 90
16-19 (N=518)	108	23.2	410	34.2	-48	-113 to -2	-40	-140 to 20	0	-	-	-
20-25 (N=105)	41	4.9	62	16.1	-230	-1332 to 24	-200	-1,470 to 40	2	-	-	-
Total (N=1,542)	163	19.0	820	28.3	-49	-108 to -6	-40	-120 to 20	559	4.1	-	-

Note.-CI=confidence interval.

*Calculations of aVE estimates based on 13-25 year-old individuals with information on all variables included in the multivariable model (n=910, see **Table A1**).

Appendix: supplementary on-line material.

Risk factors for mumps in 13-25 year-old individuals

To asses associations between case status and exposure risk factors, we used a self-administered questionnaire with information on socio-demographic status, risk factors for exposure to mumps, disease history, symptoms, and hospital stay due to mumps. Study participants aged <15 years were asked to complete the questionnaire with their parents. Information on vaccination status and disease history for measles, mumps, and rubella were taken from the medical records kept at the sanitary service of the educational institutions. The risk factor analysis was restricted to the age-groups with unvaccinated individuals, i.e. 13-25 years. In younger age-groups nearly all children had two doses of mumps vaccination. Only one individual between six and nine years of age and nobody between 10 and 12 years was unvaccinated. We explored potential risk factors in 13-25 year-old individuals unvaccinated or vaccinated with one dose of monovalent mumps vaccine and with information on all variables using univariable and multivariable logistic regression.

We included 910 individuals (57% of total study population) in the analyses. Reported contact with a mumps case and being a dormitory resident were associated with having mumps after adjusting for other variables. Participants from the college and the university faculty had a lower risk of getting mumps (**Table A1**).

Estimates of historical vaccine effectiveness in Moldova (1997-2001)

To estimate historic vaccine effectiveness (VE) we applied the "screening method"

(Reference A1), using national surveillance data whereby VE=(PPV-PCV)/(PPV*[1-PCV]), with PPV=proportion of the population vaccinated, PCV=proportion of cases vaccinated. We calculated exact 95% CIs around the PCV and entered them into the formula to obtain 95% confidence intervals (CIs) around VE estimates,. To obtain PPV estimates, the regional health authorities annually review the vaccination status of registered children from the ten youngest

birth cohorts, e.g. in 2003 PPV estimates were obtained for birth cohorts 1993-2002. We used the most recent PPV estimate for each birth cohort, e.g. the PPV estimate from 2002 for the birth cohort 1992. We used mumps surveillance data for the period 1997-2001 to estimate the VE by age-group. Data from before 1997 (incomplete data) and after 2001 (insufficient number of unvaccinated cases) were excluded.

The average PPV between 1997 and 2001 was 89%, 89%, 95% and 82% in 2, 3-6, 7-14 and 15-19 year-olds, respectively. In 1997-2001 the estimated VE for a single dose of mumps vaccine decreased from 91% in 2 year-olds to 72% in 15-19 year-olds (**Table A2**). For older age-groups PPV estimates were not available and VE could therefore not be estimated.

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A1. Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol 1993;22(4):742-6.

Figure A1: Notified mumps cases by month, Republic of Moldova, July 2007 – July 2008 (n=31,203).
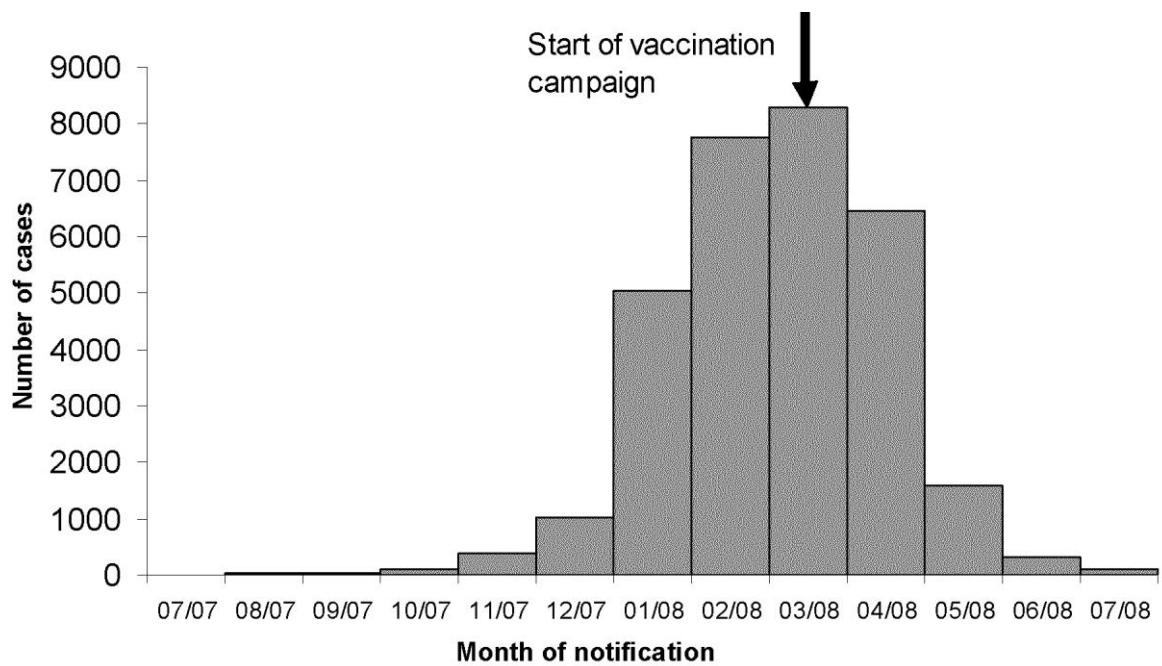
Table A1: Results of the risk factor analysis using univariable and multivariable logistic regression, cohort study, Republic of Moldova, March 2008. The models include 13-25 year-old individuals unvaccinated or vaccinated with one single dose of monovalent mumps vaccine and with information on all variables (n=910).

Risk factor	Univariable Analysis		Multivariable analysis Baseline odds=0.14 Pseudo R2=0.07	
	OR	95%CI	aOR	95%CI
Educational setting				
School 1	Ref.		Ref.	
School 2	1.7	1.1-2.6	1.1	0.7-1.9
School 3	1.4	0.9-2.1	1.0	0.7-1.6
College	1.0	0.6-1.4	0.3	0.1-0.7
University faculty	0.3	0.1-0.7	0.1	<0.1-0.5
Mumps vaccination				
Unvaccinated	Ref.		Ref.	
1 dose monovalent	1.7	1.1-2.7	1.4*	0.8-2.2*
			stratified by age-group	
13-15 years			0.7	0.2-2.4
16-19 years			1.4	0.8-2.4
20-25 years			3.0	0.6-15.7
Age-group (years)				
13-15	Ref.		Ref.	
16-19	1.5	1.1-2.1	0.9	0.2-3.5
20-25	0.4	0.2-0.8	0.4	0.1-2.7

Female sex	1.1	0.8-1.5	1.1	0.8-1.5
Risk factors for exposure				
Reporting contact with mumps case	5.6	2.8-11.3	4.0	2.0-8.2
Weekly use of public transport	1.1	0.8-1.5	1.3	0.9-1.8
Living in a dormitory	0.9	0.6-1.2	2.2	1.1-4.4
Living with ≥3 co-residents	0.8	0.6-1.1	0.8	0.5-1.1

Note: (a)OR = (adjusted) odds ratio; CI = confidence interval; Ref. = reference group.

*Overall aOR for one dose of monovalent mumps vaccine was derived from separate model that included the same co-variables.

Table A2: Proportion of population vaccinated (PPV), proportion of cases vaccinated (PCV), vaccine effectiveness (VE) estimates and 95% confidence intervals (CI) by age-group for a single dose of monovalent mumps vaccine, derived from routine surveillance data using the screening method for the period 1997-2001, Republic of Moldova.

Age (years)	PPV (%)	Cases vaccinated (n)	Cases with known vaccination status (N)	PCV (%) (n/N)	VE (%)	95%CI (%)
2	89	149	344	43	91	88-92
3-6	89	1720	4779	35	93	93-94
7-14	95	11690	15561	75	84	84-85
15-19	82	2143	3820	56	72	70-74