

1 **Supplementary information**

2 **Figure S1:** Protection conferred against lethal challenge of 5x MLD50 of either
3 pH1N1 (A/Luxembourg/46/2009) or H3N2 (A/Aichi/68) virus. Mock mice were
4 vaccinated with adjuvant only. Mice vaccinated with LAH-HBc chimeric proteins
5 showed (A and B) 100% survival after pH1N1 challenge and (C and D) 75%
6 survival after H3N2 challenge, while the mock mice all died. Error bar indicates
7 SD.

8 **Figure S2:** (A) Principle component analysis on the frequency of mutants. †:
9 corresponding to the samples with the same labeling in Fig. 4A and 5B. (B)
10 Principle component analysis on the Shannon diversity per position.

11 **Table S1:** Sample characteristics.

12 **Table S2:** Comparison of diversity at individual epitope positions. Highlighted in
13 grey are the p-values that are smaller or equal to 0.05.

14 **Table S3:** Table containing the different amino acid sequences of LAH domain
15 (55 amino acids) and the number of sequences within the individual samples.

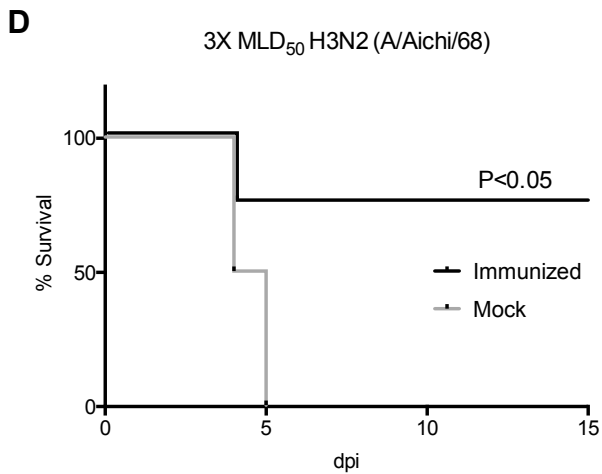
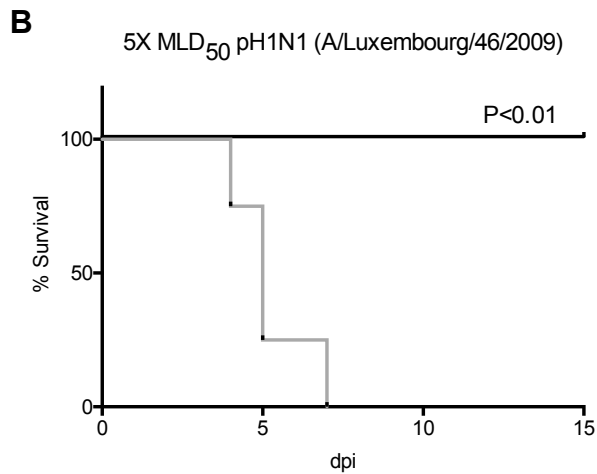
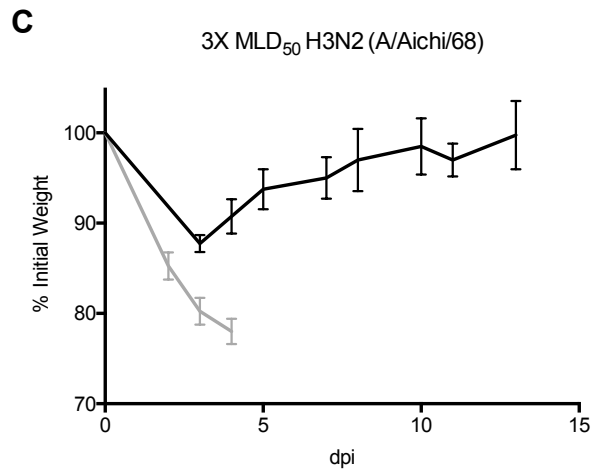
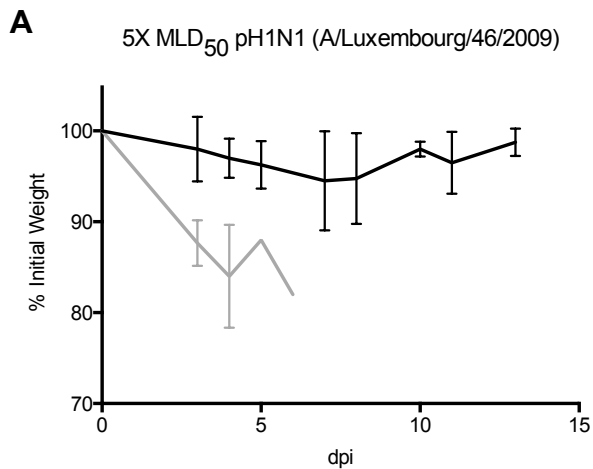
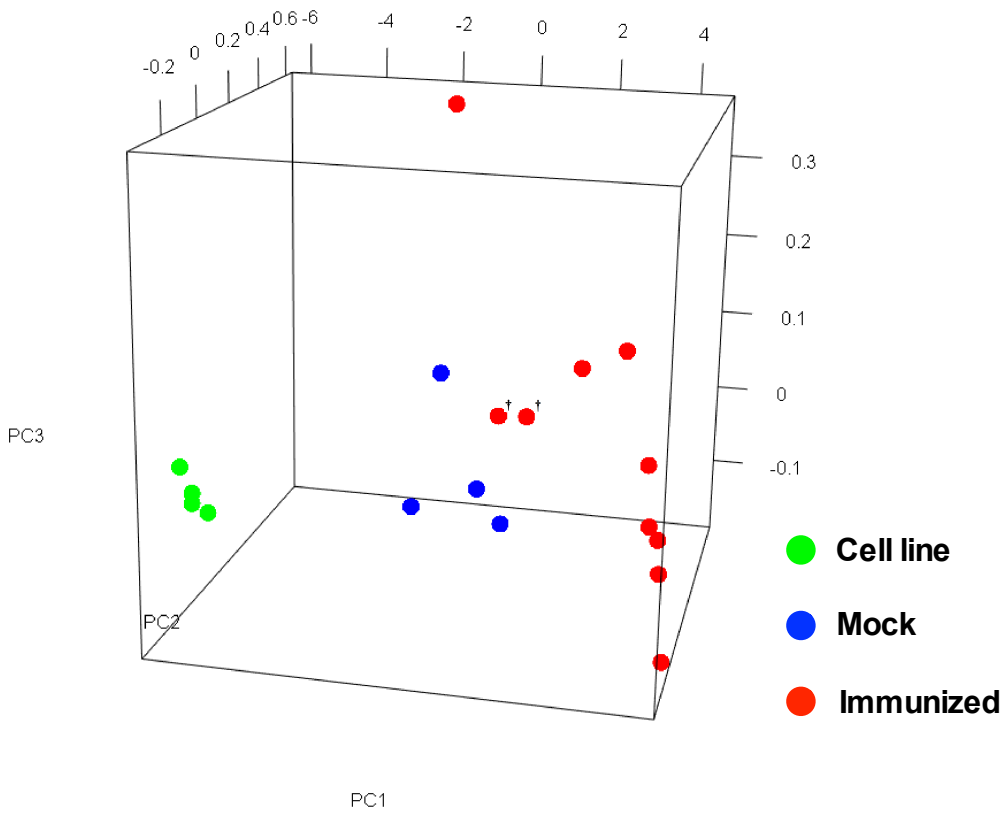
Figure S1

Figure S2

A



B

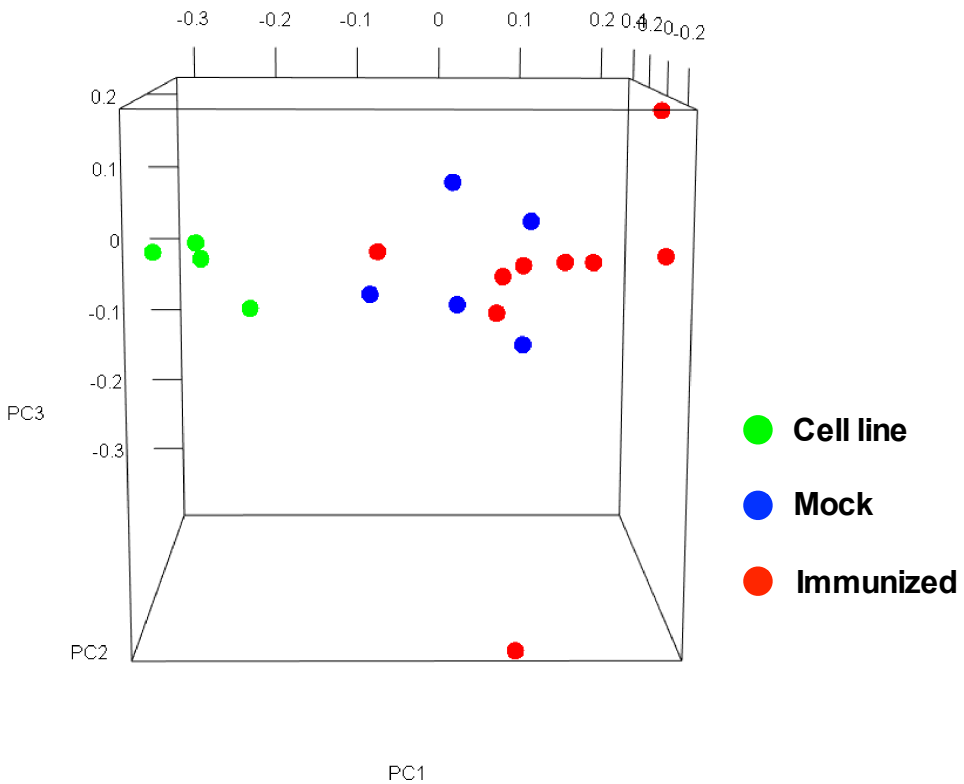


Table S1 : Sample characteristics

Sample ID	Sample type	Library input RNA (ng)	Sacrifice DPI	Total entropy (nt)	Total entropy (aa)	Lung viral load (TCID50/ml)	Raw reads	UIDs	Reads for consensus sequence	Consensus sequences	Average reads/UID	Unique consensus sequences	Average UIDs/unique consensus sequence	Average reads/unique consensus sequence	Pool N°	MID
1,1	Virus stock (wildtype virus)	100	n.a.	0,768456	0,55844187	n.a.	249062	28895	207057	19306	10,725008	319	60,52037618	649,0815047	24	7
2,1	Virus stock (wildtype virus)	100	n.a.	0,805674	0,56186719	n.a.	413227	62346	377514	46755	8,0743022	539	86,74397032	700,3970315	24	11
2,2	Virus stock (wildtype virus)	100	n.a.	0,808001	0,567291049	n.a.	384512	51099	351825	38826	9,0615824	501	77,49700599	702,245509	24	19
2,3	Virus stock (wildtype virus)	100	n.a.	0,810224	0,56844083	n.a.	478384	75522	434946	51322	8,4748451	572	89,72377622	760,3951049	24	30
1	Lung (non-immunized)	275	7	0,555852	0,394090453	1,17E+04	389408	26892	218449	8102	26,962355	147	55,11564626	1486,047619	21	11
2	Lung (non-immunized)	1375	7	0,606014	0,34190796	2,97E+04	968277	249635	418190	55685	7,5099219	537	103,6964618	778,7523277	22	19
35	Lung (non-immunized)	145	5	0,783145	0,46964991	5,18E+04	520478	17578	468695	11755	39,871969	298	39,44630872	1572,802013	26	7
36	Lung (non-immunized)	100	5	0,538169	0,334547876	2,26E+04	729269	34345	697904	13131	53,149341	199	65,98492462	3507,055276	28	30
37	Lung (non-immunized)	200	5	0,607578	0,437185145	1,01E+04	504915	18283	434872	1852	234,8121	69	26,84057971	6302,492754	30	30
79	Lung (immunized)	1750	7	0,475210	0,251287634	1,62E+02	359130	12425	327526	5014	65,322298	128	39,171875	2558,796875	21	30
80	Lung (immunized)	640	7	0,602794	0,367450867	1,62E+02	558652	13859	539592	9040	59,689381	201	44,97512438	2684,537313	22	11
11	Lung (immunized)	600	7	0,657133	0,387058732	7,12E+01	405625	18700	391768	14014	27,955473	284	49,34507042	1379,464789	22	7
27	Lung (immunized)	110	5	0,368877	0,196255209	8,97E+04	604422	15195	583742	10267	56,856141	137	74,94160584	4260,890511	26	19
28	Lung (immunized)	100	5	0,392637	0,162089965	6,82E+04	848061	95931	334904	21357	15,681229	239	89,35983264	1401,271967	26	11
29	Lung (immunized)	100	5	0,396898	0,215045413	6,82E+04	397063	27641	386600	23130	16,714224	253	91,4229249	1528,063241	28	7
30	Lung (immunized)	100	5	0,367257	0,188697023	5,40E+05	620031	40259	601034	31871	18,858335	303	105,1848185	1983,610561	28	19
31	Lung (immunized)	100	5	0,355671	0,178209204	2,26E+04	780964	8348	742711	3718	199,76089	83	44,79518072	8948,325301	30	11
32	Lung (immunized)	100	5	0,432963	0,244150093	9,36E+05	678494	19510	512667	7991	64,15555	153	52,22875817	3350,764706	30	19

Table S2

Position	76	77	78	79	80	81	82	83	84	85
cell culture vs non-immunized	0.292616	0.831553	0.478317	0.15173	0.711181	0.433241	0.009468	0.868584	0.721146	2.15E-05
cell culture versus immunized	0.148153	0.439168	0.343384	0.044034	0.268772	0.066971	0.056373	0.020627	0.513456	2.32E-06
non-immunized versus immunized	0.024443	0.852597	0.128802	0.695185	0.661709	0.913779	0.628313	0.106978	0.445411	0.026975
Position	86	87	88	89	90	91	92	93	94	95
cell culture vs non-immunized	0.409373	0.986387	0.946881	0.980912	0.325207	0.586326	0.944317	0.384279	0.432374	0.037863
cell culture versus immunized	0.356005	0.570698	0.899164	0.378814	0.995405	0.628583	0.685288	0.890213	0.817771	0.053014
non-immunized versus immunized	0.870714	0.688724	0.861248	0.693908	0.339911	0.893354	0.819628	0.307083	0.397107	0.689807
Position	96	97	98	99	100	101	102	103	104	105
cell culture vs non-immunized	0.022901	0.301015	0.865686	0.887838	0.995476	0.65968	0.929282	0.979047	0.050824	0.656383
cell culture versus immunized	0.006642	0.011795	0.06641	0.259885	0.210621	0.200475	0.846323	0.456511	0.053506	0.528095
non-immunized versus immunized	0.43637	0.043317	0.05457	0.213527	0.281193	0.69395	0.946569	0.551922	0.441355	0.856807
Position	106	107	108	109	110	111	112	113	114	115
cell culture vs non-immunized	0.647505	0.082314	0.40209	0.063615	0.441874	0.033465	0.349483	0.234523	0.989344	0.731096
cell culture versus immunized	0.497467	0.866529	0.00466	0.084784	0.091535	0.021761	0.873197	0.357405	0.515814	0.72478
non-immunized versus immunized	0.799975	0.082814	0.577504	0.99272	0.638318	0.923318	0.369203	0.116553	0.678137	0.981135
Position	116	117	118	119	120	121	122	123	124	125
cell culture vs non-immunized	0.252417	0.665063	0.789354	0.945037	0.340332	0.10876	0.077768	0.019396	0.162794	0.082165
cell culture versus immunized	0.124056	0.595786	0.760622	0.760921	0.331341	0.806525	0.203812	0.330418	0.314308	0.381881
non-immunized versus immunized	0.394991	0.921051	0.997191	0.670657	0.742202	0.095301	0.230844	0.017402	0.524808	0.354578
Position	126	127	128	129	130					
cell culture vs non-immunized	0.144042	0.434517	0.162201	0.727936	0.065676					
cell culture versus immunized	0.970594	0.872394	0.884391	0.743456	0.212188					
non-immunized versus immunized	0.229351	0.508503	0.15863	0.616044	0.273905					

Table S3: Amino acid sequences found and the number of sequences within the individual samples.

aa sequences	Sample ID (more details in Table S1)																		
	1	79	11	80	2	1.1	2.1	2.2	2.3	35	28	27	29	30	36	31	32	37	
RIENLNKKVNDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	285	58	300	219	1279	1220	3030	2516	3284	355	26	20	81	117	389	6	53	63	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	34	3	46	27	161	175	371	335	475	40	9	9	14	29	32	7	18	6	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	13	1	29	11	54	34	93	71	92	19	2	1	12	9	18	3	5	5	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	32	9	53	26	186	66	134	121	149	56	35	103	66	24	15	13	3	3	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	7467	4763	12934	8371	51611	16949	40950	33961	44916	10587	20523	9894	22254	30740	12322	3577	7628	1694	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	25	17	48	24	84	66	163	138	191	36	9	23	65	69	44	8	31	6	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	2	2	4	4	10	4	13	5	11	1	5	5	9	10	2	1	4	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	6	1	18	13	122	34	71	73	83	35	60	13	30	43	15	5	12	5	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	3	1	4	4	11	10	28	15	20	6	0	1	3	6	5	1	1	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	2	5	9	8	19	28	43	41	37	15	4	4	18	16	18	0	1	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	3	2	9	5	26	10	25	23	31	12	10	0	5	14	9	1	4	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	3	6	21	9	15	19	12	3	3	2	2	1	7	0	2	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	1	2	0	13	2	4	5	4	2	2	5	2	2	1	2	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	7	5	10	6	48	21	46	34	46	8	4	0	9	6	6	0	2	6	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	1	1	2	12	1	1	4	11	4	6	5	2	6	3	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	3	2	5	15	5	17	14	22	4	6	4	7	8	3	0	0	1	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	7	2	8	7	62	6	32	28	30	12	3	0	60	10	7	0	2	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	10	4	5	8	25	13	36	32	39	9	1	0	1	6	14	0	7	2	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	7	2	3	6	25	9	11	10	21	6	3	3	4	10	2	0	5	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	4	1	3	2	7	9	17	14	20	4	2	0	4	13	3	1	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	3	2	18	4	12	8	11	1	3	3	4	2	0	2	3	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	2	1	1	6	3	2	4	4	1	2	2	2	1	0	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	3	2	1	2	5	7	23	33	33	6	0	0	1	2	1	2	4	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	4	8	28	12	15	16	21	8	7	6	7	10	1	1	3	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	7	0	2	1	8	10	29	19	38	5	2	0	1	7	2	2	2	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	4	3	5	7	15	13	16	7	1	0	3	6	2	0	1	0	
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RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	0	0	3	3	7	5	3	1	1	1	1	0	1	1	1	1	
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RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	2	5	1	4	2	2	2	4	2	1	3	0	7	1	0	2	0	
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RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	2	0	1	1	2	1	3	2	2	1	2	7	0	0	0	2	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	3	0	12	5	19	12	16	7	4	6	7	2	3	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	3	3	4	6	13	11	12	0	2	1	0	2	6	0	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	1	1	3	2	2	6	4	0	0	1	4	3	3	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	4	0	6	1	4	3	6	2	2	6	1	1	1	0	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	4	0	0	2	9	5	7	2	7	0	2	0	1	1	1	1	3	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	2	1	1	0	2	2	2	0	1	0	2	3	2	1	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	1	1	6	2	1	2	2	0	1	1	1	0	2	3	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	5	1	6	3	10	5	8	3	2	2	2	0	4	2	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	1	2	9	2	5	7	14	2	1	1	1	0	1	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	3	0	12	1	8	6	8	3	5	2	1	5	0	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	2	0	9	6	5	8	6	2	2	0	0	2	1	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	0	2	12	1	3	1	5	3	3	0	1	2	0	1	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	2	0	3	4	4	2	2	3	0	2	1	1	0	1	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	4	1	2	4	2	3	3	5	0	0	0	4	3	2	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	2	2	5	4	2	4	6	2	0	0	0	2	0	0	0	4	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	1	0	8	6	13	10	10	4	3	1	0	4	0	1	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	3	1	2	1	2	1	4	1	1	1	1	1	0	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	3	2	6	9	10	10	17	0	1	0	1	2	2	0	2	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	1	1	3	1	4	4	3	1	1	3	1	0	0	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	8	1	1	2	3	6	3	0	1	0	1	1	0	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	3	0	1	0	9	0	6	7	2	0	1	1	2	2	0	1	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	3	2	3	4	9	5	5	2	1	0	3	0	3	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	2	0	3	0	4	3	2	0	2	1	3	0	1	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	1	2	0	1	1	1	1	0	0	0	0	1	3	1	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	2	0	8	2	4	4	3	1	1	1	0	6	0	0	4	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	0	0	2	0	2	1	4	0	3	0	4	2	1	1	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	1	0	1	2	1	3	3	0	1	1	2	0	2	0	1	0	
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RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	1	1	4	2	2	3	1	3	2	0	1	0	0	0	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	0	2	0	6	1	2	6	6	0	1	0	2	3	1	0	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	1	1	3	2	7	4	3	2	0	0	0	0	1	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	1	0	6	4	11	4	6	0	0	0	1	1	0	0	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	0	3	4	0	2	2	3	2	2	0	0	2	0	1	0	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	0	0	0	5	4	6	2	3	1	0	1	1	1	0	1	0	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	1	0	2	0	2	3	9	9	15	0	0	0	2	2	0	0	0	1	
RIENLNKKVDDGFLDIWYNAELLVLENERLDYHDSNVKNLYEKVRSQKQKNA	0	1	2	0	2</														

