RAPID RISK ASSESSMENT

Multi-country outbreak of hepatitis A virus genotype IA infections affecting EU countries in 2018

21 May 2018

Main conclusions

In 2018, a total of 42 hepatitis A cases has so far been reported by six European Union (EU) countries; cases are infected with one of two distinct hepatitis A virus (HAV) genotype IA strains. The cases were classified as either autochthonous, i.e. infected in the EU, or as travel related, i.e. with a travel history to Morocco.

Both HAV strains have historically been found to be epidemiologically associated with Morocco. However, many of the 2018 cases do not have a travel history to Morocco.

Cases were identified through sequencing of a viral RNA fragment in the overlapping region VP1/P2A. HAV strains with 1–2 nucleotide differences in this RNA region are likely to be associated with a common origin. Based on recent and historical molecular findings in returning travellers from Morocco and in a resident in Morocco, it is most likely that these strains have been circulating in Morocco since at least 2011, and that transmission in Morocco has been ongoing until very recently.

The two outbreak strains described in this document are not related to the strains associated with the 2016–2018 outbreak in the EU that is disproportionally affecting men who have sex with men (MSM) [1] or with the strains implicated in two food-borne outbreaks in EU countries in 2012–2014, which were associated with consumption of frozen strawberries and frozen mixed berries [2,3].

Although the source of infection is unknown, EU autochthonous cases are likely to have been infected through food-borne or person-to-person transmission. The relative homogeneity of the viral strains associated with the outbreak cases suggests that food-borne transmission could be associated with a single food product that is distributed in several EU countries. Epidemiological investigations are currently ongoing in some of the affected EU countries to test several hypotheses.

Considering that the source of the outbreak has not been definitively identified, there is a risk of further cases as part of this outbreak. Raising awareness among clinicians about the need for early detection and reporting is likely to help ongoing epidemiological investigations as well as reduce the risk of secondary transmission.

Suggested citation: European Centre for Disease Prevention and Control. Multi-country outbreak of hepatitis A virus genotype IA infections affecting EU countries in 2018 – 21 May 2018. Stockholm: ECDC; 2018.

Options for response

The World Health Organization (WHO) and most EU/European Economic Area (EEA) countries have been recommending hepatitis A vaccination to travellers to endemic countries for several years [4,5].

EU countries currently reporting autochthonous confirmed cases should consider interviewing such cases, not only about food exposures, but also about contacts to travellers to Morocco during the incubation period.

ECDC and the EU countries in the international outbreak investigation team will continue their joint investigation to confirm or refute the food-borne outbreak hypothesis. If the outbreak is indeed food-borne, the outbreak investigation team will attempt to identify the vehicles of infection. Multi-country descriptive and analytical epidemiological studies should ideally include a larger number of patients and thus increase the chance of obtaining conclusive results.

ECDC encourages EU/EEA public health authorities to continue sharing information on the epidemiological and microbiological investigations in the Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD).

Relevant public health information should be notified through the Early Warning and Response System (EWRS), as per Article 9 of Decision 1082/2013/EU on serious cross-border threats to health.

Source and date of request

ECDC internal decision, 4 May 2018.

Public health issue

After the EPIS FWD notification of a cluster of hepatitis A cases infected with two distinct strains in several EU/EEA countries, this risk assessment presents the early findings of this multi-country hepatitis A outbreak and sets out initial options for response.

Consulted experts

ECDC experts (in alphabetical order): Sergio Brusin, Dragoslav Domanovic, Katrin Leitmeyer, Taina Niskanen, Emmanuel Robesyn, Ettore Severi, Johanna Takkinen, Therese Westrell.

External experts (in alphabetical order of countries):

- Denmark: Sofie Midgley, Luise Müller, Sofie Gillesberg Raiser and Lasse Dam Rasmussen (Statens Serum Institut – SSI)
- France: Julie Figoni (Santé publique France)
- Germany: Kai Michaelis, Mirko Faber (Robert Koch Institute – RKI)
- Netherlands: Ingrid Friesema, Harry Vennema (National Institute for Public Health and the Environment – RIVM)
- Spain: Carmen Varela Martínez, Ana Maria Avellon Calvo (Instituto de Salud Carlos III)
- United Kingdom: Siew Lin Ngui (Public Health England – PHE).

Disease background information

Background information about hepatitis A can be found in disease fact sheets from ECDC, WHO and CDC [6-8].

In 2012–2016, 30 EU/EEA countries reported between 12 500 and 14 100 confirmed cases of hepatitis A annually (source: The European Surveillance System (TESSy)). In 2012–2016, Romania accounted for 35% of all cases in the EU/EEA; Bulgaria reported 15% of all cases. Cases were reported in all age groups, with most cases in children aged 5–14 years (36%), followed by 25–44 year-olds (21%). Male cases were more frequent than female cases, particularly in age groups 15–24 and 25–44 years (58%). The majority (89%) of infections were domestically acquired. Twenty-two EU/EEA countries reported the probable country of infection for some or all of their travel-associated cases. The most frequently reported countries of infection in 2012–2016 were Egypt (10%), Morocco (10%) and Turkey (8%). Morocco was among the top three destinations in six countries (Luxembourg, the Netherlands, Poland, Portugal, Slovenia and Spain); these six countries accounted for 71% of all cases reported from Morocco.

The annual submission of hepatitis A notifications to TESSy for the year 2017 is underway. As of 14 May 2018, 12 EU/EEA countries (Belgium, Croatia, Cyprus, the Czech Republic, Estonia, Finland, Iceland, Lithuania, Malta, the Netherlands, Norway and Sweden) have notified 1 873 cases for 2017. Nine countries reported the travel destinations of 232 travel-associated cases. Of these, 23 cases (10%), notified in the Netherlands and Sweden, were reported to have a travel history to Morocco.

Event background information

On 2 May 2018, Denmark launched an urgent inquiry in EPIS FWD about a cluster of hepatitis A virus (HAV) genotype IA infections involving two distinct HAV strains characterised through sequencing. In the following days, other EU Member States reported cases with HAV strains matching those detected in Denmark. ECDC and the affected Member States formed an international outbreak investigation team and drafted the following European outbreak case definition:

European outbreak case definition

- Autochthonous confirmed cases:
  - An EU/EEA resident with laboratory-confirmed HAV genotype IA and date of symptoms onset (or date of sampling if onset date not available or if the case is asymptomatic) on or after 1 January 2018

  and
  - without a travel history out of the EU/EEA in the 50 days before symptoms onset

  and
  - a sequence with ≥99.4% identity to one of the two HAV genotype IA outbreak strains ('DK2018_231' or 'DK2018_26731'), based on an overlapping fragment at the VP1/P2A region
- Travel-related confirmed cases:
  - An EU/EEA resident with laboratory-confirmed HAV genotype IA and date of symptoms onset (or date of sampling if onset date not available or if the case is asymptomatic) on or after 1 January 2018

  and
  - with a travel history out of the EU/EEA in the 50 days before symptoms onset

  and
  - a sequence with ≥99.4% identity to one of the two HAV genotype IA outbreak strains ('DK2018_231' or 'DK2018_267'), based on an overlapping fragment at the VP1/P2A region
- Travel-related possible cases:
  - An EU/EEA resident with laboratory-confirmed HAV infection and date of symptoms onset (or date of sampling if onset date not available or if the case is asymptomatic) on or after 1 January 2018

  and
  - with a travel history to Morocco in the 50 days before symptoms onset

  and
  - without sequencing characterisation of the viral RNA.

Event description

Epidemiological investigation

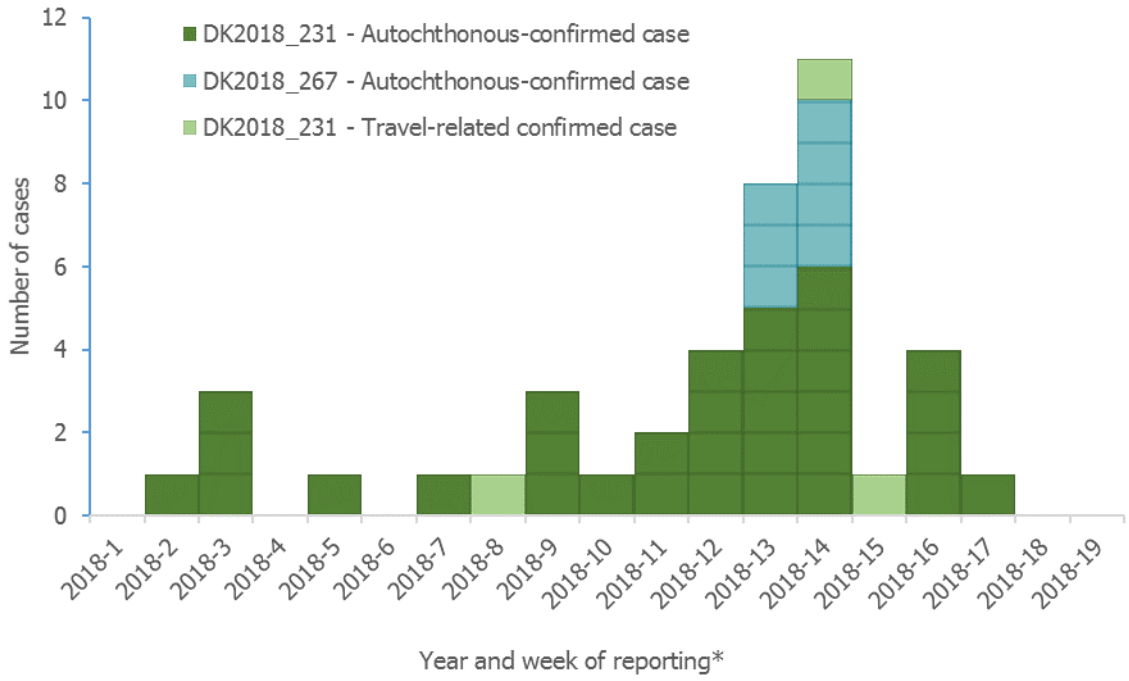
As of 11 May 2018, a multi-country outbreak has been verified in six EU Member States. Case numbers, based on the European outbreak case definition (see above), are as follows: 42 confirmed cases, 50 possible cases (Table 1).

Table 1. Distribution of confirmed hepatitis A cases by reporting country, case classification and strain, European Union, 2018 (as of 11 May 2018)

Reporting country	Autochthonous confirmed cases		Travel-related confirmed cases		Travel-related possible cases	Total
	DK2018_231	DK2018_267	DK2018_231	DK2018_267		
Denmark	5	3	1	0	0	**9**
France	0	0	1	0	23	**24**
Germany	0	0	1	0	18	**19**
Netherlands	4	4	0	0	0	**8**
Spain	1	0	0	0	9	**10**
United Kingdom (England and Wales)	22	0	0	0	0	**22**
Total	**32**	**7**	**3**	**0**	**50**	**92**

The 42 confirmed outbreak cases had a median age of 31 years (interquartile range: 17–48); 19 were females. Information on hospitalisation is available for 19 cases, and 13 of these cases were reported as hospitalised. No deaths have been reported so far. Three cases were reported with a travel history to Morocco during their incubation period. Between weeks 2 and 11 of 2018, the number of outbreak-confirmed cases ranged between one and three cases. Since then, the number of possible and confirmed cases has rapidly increased, with a peak of 11 cases in week 14 of 2018 (Figure 1). Ten of those cases had no travel history.

Figure 1. Distribution of confirmed hepatitis A outbreak cases by strain, travel history and week of reporting, European Union 2018 (n=42; as of 11 May 2018)

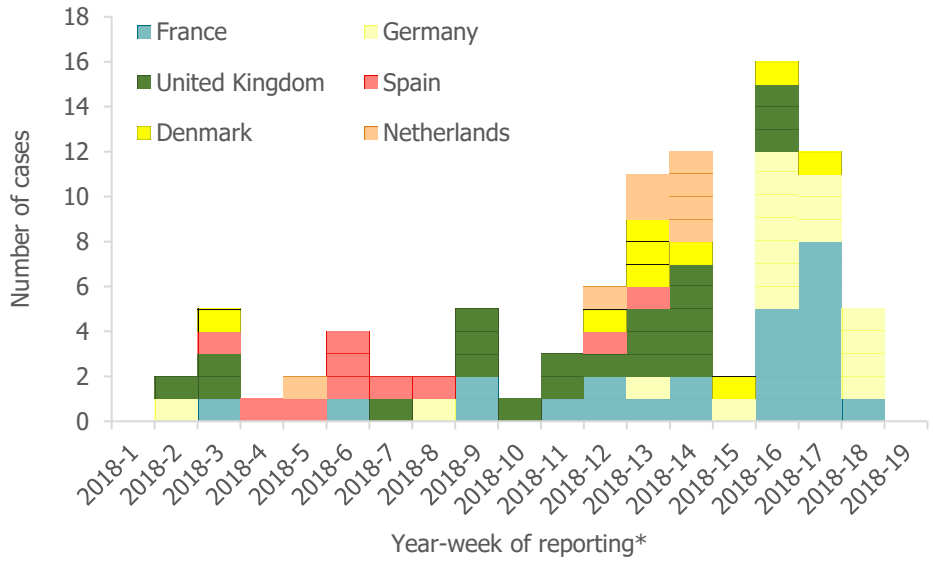


** If week of onset missing: week of sampling or week of receipt in reference laboratory*

The 50 possible outbreak cases had a median age of 32 years (interquartile range: 23–49), and 27 were females; information on hospitalisation is available for 46 cases, and 26 of these cases were reported as hospitalised. No deaths have been reported so far. As per the case definition, all cases were reported with a travel history to Morocco. Twenty-eight of the 50 possible cases were reported between weeks 16 and 18 of 2018. Possible cases were reported only by France, Germany and Spain. Possible cases from France and Germany were mostly reported in weeks 16 to 18 of 2018 (Figure 2).

Only Germany reported an increase of hepatitis A cases with a travel history to Morocco in 2018, compared with the number of hepatitis A cases with a travel history to Morocco in the same period of the previous years; the number of such cases in France and Spain was not considered higher than in previous years.

Figure 2. Distribution of possible and confirmed hepatitis A outbreak cases by country and week of reporting, European Union 2018 (n=91; as of 11 May 2018)



** If week of onset missing: week of sampling or week of receipt in reference laboratory*

Note: Case numbers do not reflect one additional possible case reported in 2018

Microbiological investigation

The sequences of the viral RNA fragment in the VP1/P2A region of the two strains 'DK2018_267' and 'DK2018_231' are available in the Annex. For 'DK2018_267'. Denmark also released a fragment of the VP1 region. The VP1/P2A junction is known to be one of the most variable regions of the HAV genome and therefore allows good resolution when comparing sequences. Comparing the overlapping fragment at the VP1/P2A junction, the two HAV strains have about 97% identity, which makes the two HAV strains distinct. Both strains were recently identified in Morocco. These strains had also been identified in the past in different EU countries, mostly in returning travellers from Morocco.

The 'DK2018_231' strain, or its close variants (up to two nucleotides of difference), was identified in 35 confirmed cases (Table 1), three of which were those reported with travel history to Morocco; one of the cases fell ill during the stay in Marrakech. These three cases were infected with a strain with 100% identity to the Danish representative strain.

The 'DK2018_267' strain was identified in seven confirmed autochthonous cases from Denmark and the Netherlands, all identified in week 13 and 14 of 2018.

In addition, France reported a female patient resident in Morocco (Casablanca) infected with a strain closely related to 'DK2018_267'. In accordance with the European outbreak case definition, this patient was not counted as an outbreak case because she is not an EU/EEA resident.

Through EPIS, Italy, the Netherlands, Sweden and the United Kingdom reported historical cases with the two outbreak strains or their close variants. At least 20 such cases were detected between 2011 and 2017, mostly in patients with a travel history to Morocco.

The United Kingdom also reported other strains identified in 2018 that are closely related to the 'DK2018_231' strain, but not within the variability allowed by the case definition, mostly in cases without a travel history.

ECDC threat assessment for the EU

In 2018, six EU countries have so far reported 42 hepatitis A cases, each infected with one of two distinct hepatitis A virus strains. The majority of these cases (39) were infected in the EU, while three cases had a travel history to Morocco.

The two outbreak strains are most likely originating from Morocco: these two strains have been detected on several occasions in residents and European travellers returning from Morocco since 2011.

Morocco is classified as a country with intermediate hepatitis A endemicity [9,10]. Areas at intermediate endemicity are characteristically affected by recurrent, large hepatitis A outbreaks. As of 11 May 2018, no information is available about the current hepatitis A transmission situation in Morocco. Based on the available information, it is not possible to say whether Morocco is currently experiencing hepatitis A outbreaks or increased transmission. The

outbreak strains have been widely circulating in the past years and, at least for France and the Netherlands, Morocco traditionally accounts for a large proportion of travel-related cases [11].

The affected EU countries have very low hepatitis A endemicity and a large part of their population is susceptible to HAV infection [5]. HAV transmission through food-borne outbreaks has often been reported in the EU, in some instances involving large and prolonged outbreaks. The most recent multi-country food-borne outbreaks, reported in 2013 and 2014, were associated with consumption of frozen berries [2,3]. Fresh strawberries were also implicated in an outbreak affecting EU/EEA travellers to Egypt in 2012–2013 [12]. The current outbreak strains are distinct from the strains implicated in these previous food-borne outbreaks.

In low and very low endemicity settings, HAV transmission has also been documented as occurring through returning travellers (via person-to-person transmission, food handling or through substances of human origin (SOHO)), particularly in those travellers that had visited family and friends in countries at intermediate or high endemicity, or through recently adopted children, with child care facilities playing an important role in spreading the infection following both kind of importation events [13,14].

A very large outbreak of hepatitis A disproportionally affecting men who have sex with men (MSM) has been ongoing in the EU/EEA since 2016, reflecting the fact that transmission during sexual practices is also common in MSM [1].

Because autochthonous cases with (nearly) identical strains are found in different EU countries, it is possible that these cases were exposed to the same vehicle of infection distributed in different EU countries. The distribution of the two outbreak strains in time and place may also reflect the fact that cases were actually part of two different events: cases infected with 'DK2018_231' were reported in most affected EU countries between January and April 2018, while those infected with 'DK2018_267' were reported only in Denmark and in the Netherlands with symptom onsets in weeks 13 and 14–2018 while those infected with 'DK2018_267' were reported only in Denmark and in the Netherlands with symptom onsets in weeks 13 and 14–2018.

The distribution of confirmed and possible cases initially followed a common pattern: reported weekly case numbers were low until week 12–2018. In weeks 13 and 14, the number of confirmed outbreak cases peaked. Possible outbreak cases infected in Morocco, however, peaked in weeks 16 and 17. It is therefore possible that additional cases, both confirmed and possible, will be reported in the coming weeks.

In addition, some of the confirmed cases may be directly or indirectly linked with travel to Morocco. In this case, secondary transmission in the EU could have occurred from primary cases, either through food handling or through direct person-to-person transmission (including via SoHO, e.g. blood transfusion or tissue/organ donation or sex). Such secondary cases should be excluded from studies which test the hypothesis of an ongoing multi-country food-borne HAV outbreak.

So far, no severe complications in outbreak cases have been reported to ECDC. Hepatitis A is often asymptomatic in children, but the severity of the symptomatic infection increases with age. Elderly people, pregnant women and people with suppressed immune systems are at risk of severe disease, hospitalisation, hepatic coma, and death [15].

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter with their respective advantages and disadvantages. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

References

1. European Centre for Disease Prevention and Control. Epidemiological update: hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men, 23 Mar 2018. Stockolm: ECDC; 2018. Available from: https://ecdc.europa.eu/en/news-events/epidemiological-update-hepatitis-outbreak-eueea-mostly-affecting-men-who-have-sex-men-1.
2. Nordic Outbreak Investigation Team C. Joint analysis by the Nordic countries of a hepatitis A outbreak, October 2012 to June 2013: frozen strawberries suspected. Euro Surveill. 2013 Jul 4;18(27).
3. Severi E, Verhoef L, Thornton L, Guzman-Herrador BR, Faber M, Sundqvist L, et al. Large and prolonged food-borne multistate hepatitis A outbreak in Europe associated with consumption of frozen berries, 2013 to 2014. Euro Surveill. 2015 Jul 23;20(29):21192.
4. WHO position paper on hepatitis A vaccines – June 2012. Releve epidemiologique hebdomadaire. 2012 Jul 13;87(28/29):261-76.
5. Carrillo-Santisteve P, Tavoschi L, Severi E, Bonfigli S, Edelstein M, Bystrom E, et al. Seroprevalence and susceptibility to hepatitis A in the European Union and European Economic Area: a systematic review. The Lancet Infectious diseases. 2017 Oct;17(10):e306-e19.
6. Centers for Disease Control and Prevention. Viral hepatitis – hepatitis A information [internet]. Atlanta: CDC; 2017. Available from: https://www.cdc.gov/hepatitis/hav/index.htm.
7. European Centre for Disease Prevention and Control. Factsheet about hepatitis A [internet]. Stockholm: ECDC; 2017. Available from: https://ecdc.europa.eu/en/hepatitis-A/facts.
8. World Health Organization. Hepatitis A [internet]. Geneva: WHO; 2017. Available from: http://www.who.int/en/news-room/fact-sheets/detail/hepatitis-a.
9. Koroglu M, Jacobsen KH, Demiray T, Ozbek A, Erkorkmaz U, Altindis M. Socioeconomic indicators are strong predictors of hepatitis A seroprevalence rates in the Middle East and North Africa. Journal of infection and public health. 2017 Sep - Oct;10(5):513-7.
10. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010 Sep 24;28(41):6653-7.
11. Sane J, de Sousa R, van Pelt W, Petrignani M, Verhoef L, Koopmans M. Risk of hepatitis A decreased among Dutch travelers to endemic regions in 2003 to 2011. J Travel Med. 2015 May-Jun;22(3):208-11.
12. Sane J, MacDonald E, Vold L, Gossner C, Severi E. Multistate food-borne hepatitis A outbreak among European tourists returning from Egypt – need for reinforced vaccination recommendations, November 2012 to April 2013. Euro Surveill. 2015 Jan 29;20(4).
13. Abdulla RY, Rice MA, Donauer S, Hicks KR, Poore D, Staat MA. Hepatitis A in internationally adopted children: screening for acute and previous infections. Pediatrics. 2010 Nov;126(5):e1039-44.
14. Kumbang J, Ejide S, Tedder RS, Ngui SL. Outbreak of hepatitis A in an extended family after importation by non-immune travellers. Epidemiology and infection. 2012 Oct;140(10):1813-20.
15. Koff RS. Hepatitis A. Lancet. 1998 May 30;351(9116):1643-9.

Annex

Sequence of the viral RNA fragment of the strain 'DK2018_231':

GATGAATATTTGTCCTTTAGTTGTTACTTGTCTGTTACAGAACAATCAGAGTTTTATTTTCCTAGAGCTCCATTGAATTC
AAATGCCATGTTGTCTACTGAGTCTATGATGAGTAGAATTGCAGCTGGAGACTTGGAGTCATCAGTGGATGATCCTA
GATCAGAGGAGGACAGGAGATTTGAGAGTCATATAGAATGTAGAAAACCATACAAAGAATTGAGATTAGAGGTTGGG
AAACAAAGACTCAAATATGCTCAGGAAGAGTTGTCAAATGAAGTGCTTCCACCTCCTAGGAAAATGAAAGGGGTTTTT
TCCCAGGCTAAAATTTCTCTTTTTTATACTGAGGAGCATGAAATAATGAAATTTTCTTGGAGAGGAGTGACTGCTGAT
ACTAGAGCTTTGAGAAGATTTGGATTCTCTATGGCCGCTGGTAGAAGT

Sequence of the viral RNA fragment of the strain 'DK2018_267':

TAATGTTTATCTTTCAGCAATTAATTTGGAATGTTTTGCTCCTCTTTATCATGCTATGGATGTTACCACACAGGTTGGA
GATGATTCAGGGGGTTTTTCAACAACAGTTTCTACAGAGCAGAATGTTCCTGATCCTCAAGTTGGCATAACAACCATG
AGGGACCTAAAAGGGAAAGCCAATAAGGGGAAGATGGATGTTTCAGGAGTGCAAGCGCCTGTGGGAGCTATCACAA
CAATTGAGGATCCAGTTTTAGCAAAGAAAGTGCCTGAGACATTTCCTGAACTGAAGCCTGGAGAGTCCAGACATACA
TCAGATCACATGTCTATTTATAAATTCATGGGAAGGTCTCATTTTCTGTGCACTTTTACCTTCAATTCAAATAATAAAGA
GTACACATTTCCAATAACTTTGTCTTCAACCTCTAATCCTCCTCATGGTTTACCATCAACATTAAGGTGGTTTTTCAATT
TGTTTCAGTTGTATAGAGGACCTTTGGATTTGACAATTATCATCACAGGAGCTACTGATGTTGATGGTATGGCCTGGT
TTACTCCAGTAGGCCTTGCTGTCGACACCCCTTGGGTGGAAAAGGAGTCAGCTTTGTCTATTGATTATAAAACTGCCC
TTGGAGCTGTTAGATTTAATACAAGAAGAACAGGGAACATTCAGATTAGATTGCCATGGTATTCTTATTTGTATGCCG
TGTCTGGAGCGTTGGATGGCTTGGGAGATAAGACAGATTCYACATTTGGATTGGTTTCTATTCAGATTGCAAATTATA
ATCATTCTGATGAATATTTGTCTTTTAGTTGTTACTTGTCTGTCACAGAACAATCAGAGTTTTATTTTCCTAGAGCTCCA
TTGAATTCAAATGCTATGTTGTCCACTGAGTCTATGATGAGTAGAATTGCAGCTGGTGATTTGGAGTCATCAGTGGAT
GATCCTAGATCAGAGGAGGACAGAAGATTTGAGAGTCATATAGAATGTAGGAAACCATACAAAGAACTGAGATTGGA
GGTTGGGAAACAAAGACTCAAATATGCTCAGGAAGAATTGTCAAATGAAGTGCTTCCACCTCCTAGGAAAATGAAAG
GGGTTTTTTCCCAGGCTAAAATTTCTCTTTTTTATACTGAGGAGCATGAAATAATGAAATTTTCTTGGAGAGGAGTGAC
TGCTGATACTAGAGCCTTGAGAAGATTTGGATTCTCTATGGCCGCTGGTAGAAGT