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Médecine et maladies infectieuses
Médecine et maladies infectieuses 44 (2014) 412–416

Original article

Case fatality rates of Ebola virus diseases: A meta-analysis of World Health Organization data

Taux de létalité due aux maladies à virus Ébola : méta-analyse des données de l'Organisation mondiale de la santé

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Received 15 April 2014; received in revised form 20 June 2014; accepted 6 August 2014
Available online 2 September 2014

Abstract

Objective. – Our objective was to estimate the case fatality rates of Zaire, Sudan, and Bundibugyo Ebola species, responsible for sometimes-lethal hemorrhagic fevers.

Methods. – We performed a meta-analysis of World Health Organization data on outbreaks of infections due to theses species.

Results. – Twenty outbreaks, including the current one, were studied. The estimated case fatality rate was 65.4% (CI 95% [54.6%; 75.5%]) and varied among the outbreaks. A species effect was identified, with a higher case fatality rate for the Zaire species than for Sudan and Bundibugyo species. The case fatality rate of the Zaire species tended to decrease with time.

Conclusion. – The case fatality rates associated with these 3 species was high. A great variability was observed. It could be explained partly by a species effect and by the decrease of Zaire species case fatality rate, with time.

Keywords: Ebola; Case fatality rate; Meta-analysis

Résumé

Objectif. – Estimer le taux de létalité due aux espèces Ébola Zaïre, Soudan, et Bundibugyo à l'origine de fièvre hémorragiques parfois fatales.

Méthodes. – Méta-analyses des données de l'OMS relatives aux différents épisodes liés à ces virus.

Résultats. – Vingt épisodes, dont 1 actuel, ont été relevés. Leur méta-analyse a démontré une létalité élevée de 65,4 % (IC 95 % [54,6 % ; 75,5 %]). Ce taux est très variable selon les épisodes. Un effet de l'espèce est retrouvé, avec un taux de létalité plus important pour l'espèce Zaïre que pour les espèces Soudan et Bundibugyo. Une tendance à la diminution au cours du temps est mise en évidence pour l'espèce Zaïre.

Conclusion. – Le taux de létalité associé à ces 3 espèces est élevé. Une variabilité importante est observée. Elle est expliquée en partie par l'effet de l'espèce et la diminution de la létalité au cours du temps pour l'espèce Zaïre.

Mots clés : Ébola ; Taux de létalité ; Méta-analyse

1. Introduction

The Ebola virus disease is a hemorrhagic fever due to a virus of the same name, of the *filoviridae* family, and of the *Filovirus* genus [1]. There are 5 species of the virus: Bundibugyo, Zaire, Sudan, Reston, and Taï Forest (previously called Ebola Cote d'Ivoire) [2,3]. The 3 first species cause epidemics in Africa and

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http://dx.doi.org/10.1016/j.medmal.2014.08.005
0399-077X/

Table 1
Number of cases and deaths, case fatality rates, and species among outbreaks of hemorrhagic fevers due to Ebola virus in Africa between 1976 and 2014 (WHO data [3,8]).
Nombre de cas, de décès, taux de létalité et espèce en cause dans les épisodes de fièvres hémorragiques à virus Ébola en Afrique entre 1976 et 2014 (données OMS [3,8]).

Country	Year	Species of virus	Number of cases	Number of death	Case fatality rate (%)
Sudan	1976	Sudan	284	151	53
Democratic Republic of Congo	1976	Zaire	318	280	88
Democratic Republic of Congo	1977	Zaire	1	1	100
Sudan	1979	Sudan	34	22	65
Gabon	1994	Zaire	52	31	60
Democratic Republic of Congo	1995	Zaire	315	254	81
South Africa	1996	Zaire	1	1	100
Uganda	2000	Sudan	425	224	53
Congo	2001	Zaire	59	44	75
Gabon	2001	Zaire	65	53	82
Sudan	2004	Sudan	17	7	41
Congo	2005	Zaire	12	10	83
Uganda	2007	Bundibugyo	149	37	25
Democratic Republic of Congo	2007	Zaire	264	187	71
Democratic Republic of Congo	2008	Zaire	32	14	44
Uganda	2011	Sudan	1	1	100
Democratic Republic of Congo	2012	Bundibugyo	57	29	51
Uganda	2012	Sudan	7	4	57
Uganda	2012	Sudan	24	17	71
Liberia-Guinea-Sierra Leone (ongoing)	2014	Zaire	453	245	54

severe hemorrhagic diseases, with high case fatality rates. No human death due to the 2 other species has ever been reported. The Reston species causes death in primates, but is less virulent than the Zaire and Sudan species [4].

The World Health Organization (WHO) has reported several outbreaks of Ebola virus infections since its discovery in 1976 [3,5]. An outbreak is ongoing in Guinea, Liberia, and in Sierra Leone [5,6]. The case definition, often difficult during these epidemics, makes it difficult to estimate the case fatality rate [7,8]. We had for objective to estimate the case fatality rate due to Ebola virus Bundibugyo, Zaire, and Sudan species, with a meta-analysis of the WHO data on the various epidemics related to the virus.

2. Methods

A meta-analysis of case fatality WHO data was performed using a Freeman-Tukey (double arcsine) transformation [9] so as to stabilize the variance of proportions. The number of deaths was compared to the number of suspected or confirmed cases, to determiner the case fatality rate for every outbreak [10]. A random effect model was used according to DerSimonian-Laird's method in case of heterogeneousness [11]. Sensitivity analyses were performed by removing epidemics with a low number of cases (< 10) and the ongoing epidemic. A cumulative meta-analysis was used to assess the stabilization of the case fatality rate with time. Sub-group analyses were performed by species. Finally, the species effect and the time effect were investigated by using univariate and multivariate linear meta-regression models for changed proportions. A linear trend was investigated globally for the time effect then for every viral species after having tested the hypothesis of linearity by using fractional polynomials. The R [12] ("meta" [13] and "metafor" packages) and Stata [14] (fracpoly function) software were used for the statistical analyses.

3. Results

Nineteen outbreaks were identified between 1976 and 2012 (WHO data [3]), with at least 1 case, and at most 425 cases. Among them, 2118 cases and 1367 deaths were recorded. Another recent outbreak concerned, as of June 10, 2014, 453 cases and 245 deaths [15]. The data for these outbreaks is presented in Table 1.

The meta-analysis of the various outbreaks revealed a high case fatality rate of 65.4% (CI 95% [54.6%; 75.5%]) (Fig. 1). The heterogeneousness was very important ($I^2 = 94\%$). The sub-group analyses revealed a greater mortality for the Ebola Zaire species (76%, CI 95% [63%; 87%]) than for the Sudan species (55% CI 95% [50%; 59%]) and Bundibugyo species (37%, CI 95% [14%; 63%]).

The heterogeneousness was low for the Sudan species; it was high for the Zaire and Bundibugyo species. The estimations were made with 2 outbreaks only for the Bundibugyo species. The sensitivity analyses, made by removing epidemics with a low number of cases (< 10) and ongoing epidemics yielded similar results.

Using fractional polynomials for the regressions according to the year did not allow ruling out the hypothesis of linearity. The multivariate meta-regression model did not allow demonstrating any significant effect of the year of epidemic onset on the case fatality rate, even if the case fatality rate decreased significantly ($P = 0.005$) with time in univariate regression model (Table 2). But it confirmed the species effect. The Zaire species