

Key Message

The nasal administration route has garnered substantial interest for vaccination and nose-to-brain delivery via the olfactory region. Current swirl nozzle devices deliver less than 5-10% of their dose to the target region. A novel pre-filled syringe soft mist nasal spray delivers over 40% to the olfactory region, significantly improving delivery efficiency for N2B applications, with the ability to target regions of interest for nasal vaccines, such as the posterior nasal cavity.

Background

- Inhaled delivery via the nasal tract can offer a suitable route for systemic and local drug delivery. In the markets there is increased interest to target the central nervous system via nasal delivery, however there are requirements for the drug to be delivered in the olfactory region and/or the trigeminal nerve (posterior nasal cavity).
- Current nasal spray technology is based swirl-nozzles, which are not suitable to target delivery to specific regions in the nasal cavity for nasal vaccination or nose-to-brain delivery
- Controlling particle size distribution and other plume characteristics such as plume velocity¹ and plume shape is essential for delivery towards the nasal cavity

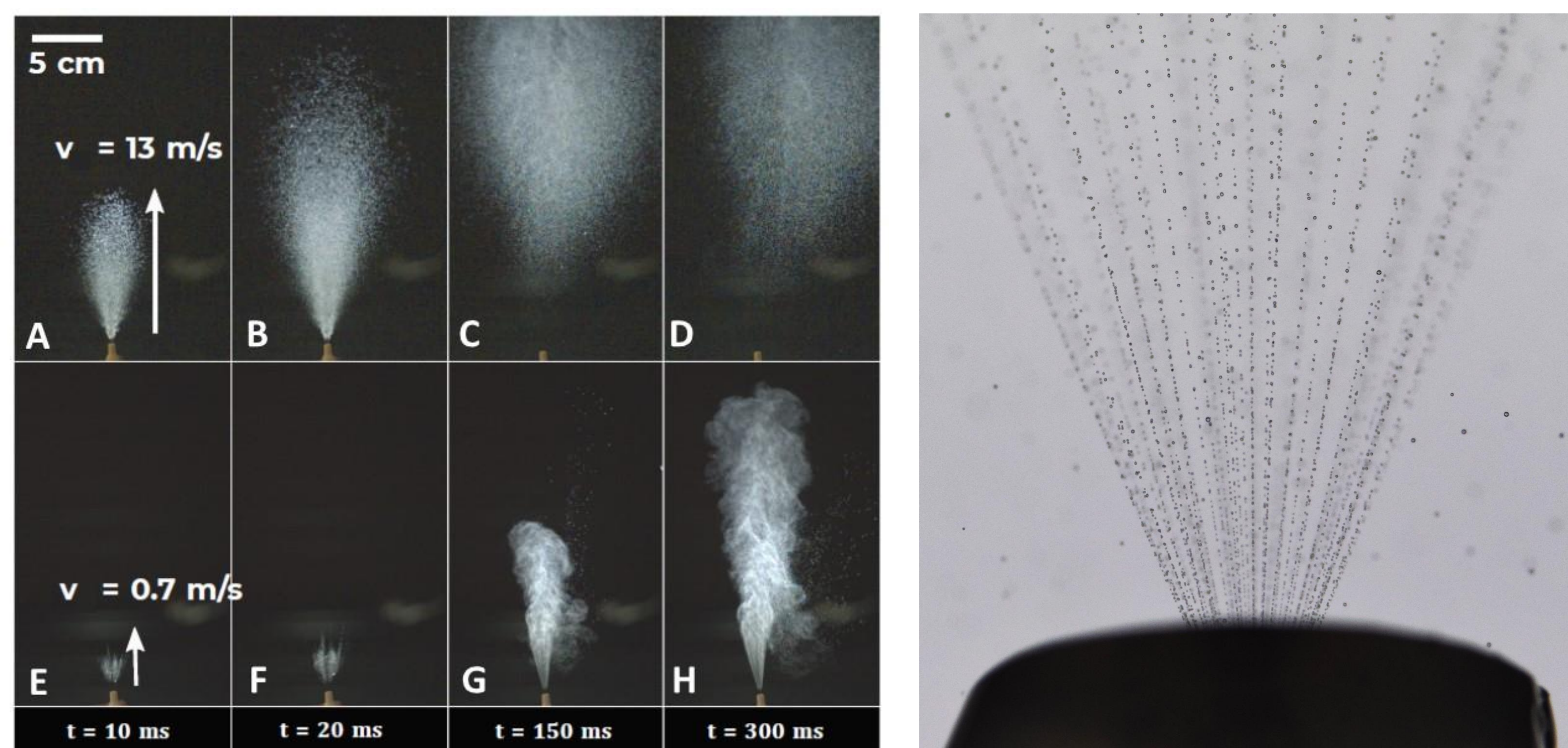


Figure 1: (a) High speed imaging standard nasal spray (A – D) and soft nasal spray (E– H) including plume velocity measurement. (b) High speed image of detailed plume shape controlled by the micro pores

- Current swirl-based nozzle systems have limited controllability to these parameters and are strongly affected by the formulation properties and human control of the actuation velocity.
- In this research two off-the-shelf single use delivery devices have been compared in a head-to-head comparison study with a novel pre-filled syringe nasal spray facilitating Rayleigh jet principle.



Figure 2: PFS Soft Mist Nasal Spray (a) consisting of an Alba® EZ®-fill glass syringe (Stevanato Group, IT) and the nano-tech spray nozzle (b) (Medspray BV, NL) embedded in a bespoke designed syringe closure. (c) design options

Methods

- The MAD300 (Teleflex), Accuspray (BD) and Resyca's PFS-nasal spray platform were filled with placebo formulations specific for the anticipated studies with each 150µL dosing volume.
- Aerosol plume characterisation measurements (PSD) were determined by a Malvern Mastersizer S laser diffraction system with an open bench method (10cm from laser, 5cm from lens) by manual operation of the spray devices
- In-vitro deposition studies have been performed with a fluorescence marker as delivered in a nasal cast model (Koken cast)^{1,2}. Photographs of the deposition profile have been taken under UV light showing the profile of the fluorescent marker and are analysed by 2D mapping of the deposition profile based upon the 3D nasal cast. For different regions of interest (ROIs) the amount of pixels are calculated and compared with the actual pixels exited by the fluorescence marker to do a quantitative analysis for the regional surface coverage of the ROI. Conditions during the deposition study are matching with the intended use of the three different products. In all cases 150µL is being dispensed in an individual measurement with manual actuation.

Results

	Dv10 [µm]	Dv50 [µm]	Dv90 [µm]	N *
MAD300 (Teleflex)	37.9 (7.6)	80.2 (18.2)	146.8 (18.6)	75
AccuSpray (BD)	197.8 (113.6)	402.2 (82.4)	630.9 (62.4)	3
PFS-nasal (Resyca)	12.4 (1.3)	23.1 (2.0)	39.7 (10.6)	25

Table 1: Particle size distribution Dv10, Dv50 and Dv90 for the tested devices; mean (SD). * different sample sizes due to availability of the test materials and refillability of the MAD300

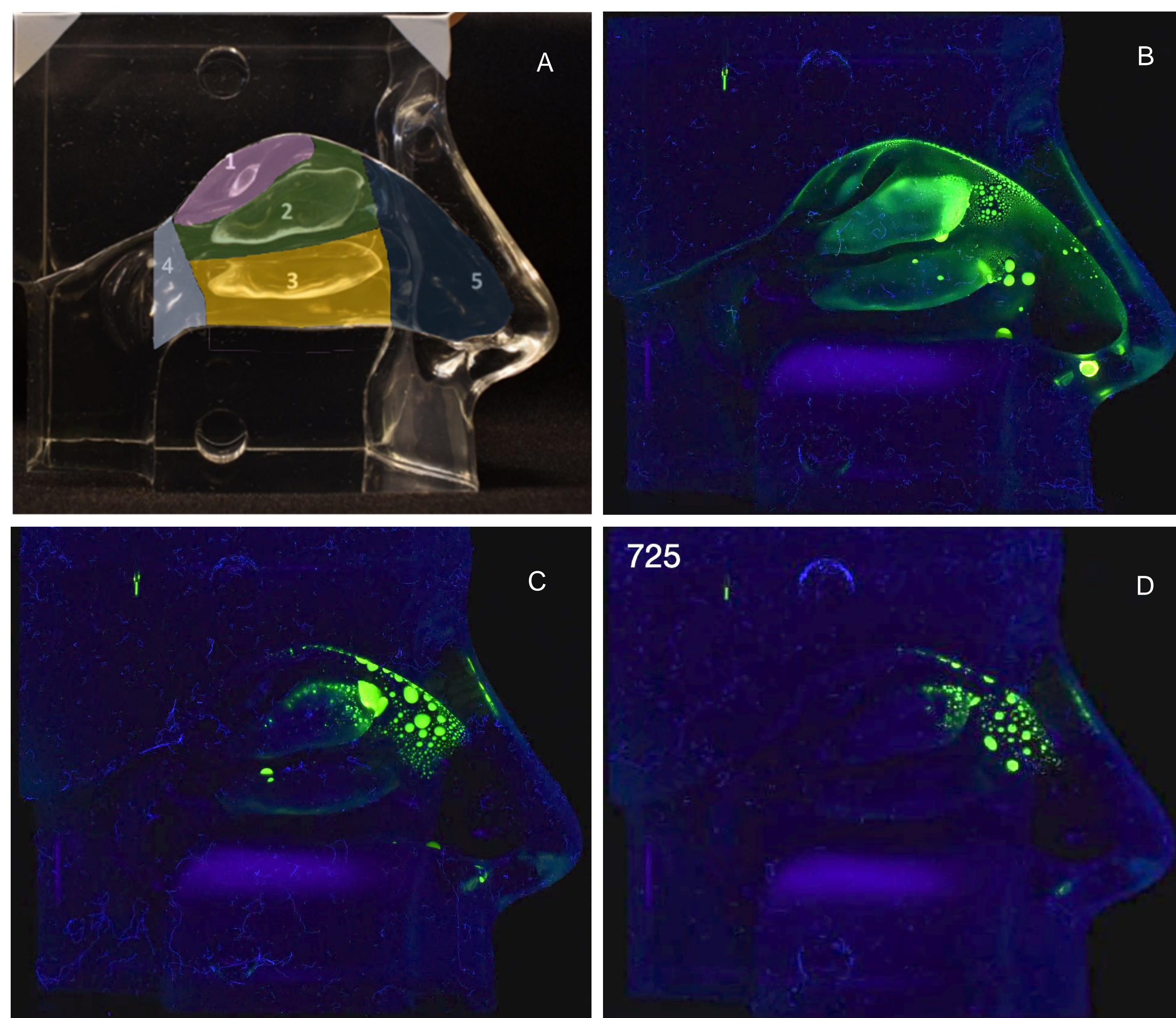


Figure 3: (A) pre-defined ROIs in the Koken nasal cast (B) Deposition profile with the PFS-soft mist nasal (Resyca) (C) Deposition profile with AccuSpray (D) Deposition profile with Teleflex MAD300

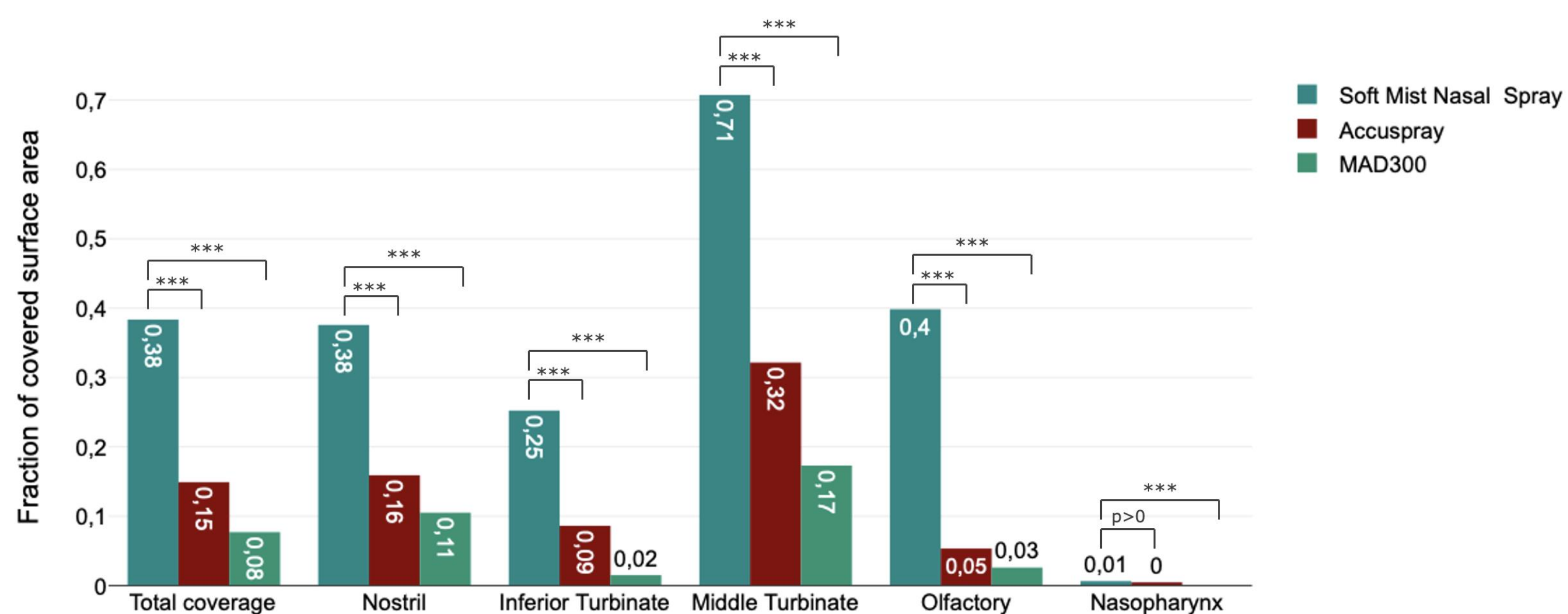


Figure 4: Regional and total surface coverage based upon 2D image analysis of the fluorescent deposition profile.

Conclusion

This study demonstrated that a soft mist nozzle based upon Rayleigh jet breakup can effectively target different ROIs in the nasal cavity. Significant higher surface coverage is observed in all regions, including the olfactory region, which opens potential access towards the central nervous system (CNS), except the nasopharynx.

Nasal sprays based on swirl nozzles, due to the higher plume velocity¹ and larger droplet sizes, primarily deposit in the anterior nasal cavity, while the soft mist nasal spray can penetrate into the posterior nasal cavity.

- D'Angelo, D.; Kooij, S.; Verhoeven, F.; Sonvico, F.; van Rijn, C. Fluorescence-enabled evaluation of nasal tract deposition and coverage of pharmaceutical formulations in a silicone nasal cast using an innovative spray device. *J. Adv. Res.* 2023, 44, 227–232.
- Zhang, M.X.; Verhoeven, F.; Ravensbergen, P.; Kooij, S.; Geoffrion, R.; Bonn, D.; van Rijn, C.J.M. Improved Olfactory Deposition of Theophylline Using a Nanotech Soft Mist Nozzle Chip. *Pharmaceutics* 2024, 16, 2